LONG-TERM PLASTICITY WITHIN THE HUMAN SENSORIMOTOR CORTEX

Thesis
presented to the Faculty of Arts
of the University of Zurich

for the degree of Doctor of Philosophy

by

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Accepted in the summer semester 2006
on the recommendation of

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Zurich 2007

La labor de un pianista [. . .] es inaccesible para el hombre ineducado ya que la adquisición de nuevas habilidades requiere muchos años de práctica mental y física. Para entender plenamente este complejo fenómeno se hace necesario admitir, además del refuerzo de vias orgánicas reestablecidas, la formación de vias nuevas por ramificación y crecimiento progresivo de la arborización dendrítica y terminales nerviosas.

Santiago Ramón y Cajal (1904)
Textura del SistemaNervioso
(p. 296)

The labor of a pianist [. . .] is inaccessible for the uneducated man as the acquisition of new skill requires many years of mental and physical practice. In order to fully understand this complex phenomenon it becomes necessary to admit, in addition to the reinforcement of pre-established organic pathways, the formation of new pathways through ramification and progressive growth of the dendritic arborization and the nervous terminals.

(English translation by A. Pascual Leone, 2005)

Irish story tellers always begin this way:
„It was not in my time,
not in your time, not in anybody's time."
The story I am about to tell also belongs to no time
because it relates to the greatest mystery of all time: The brain.

[A. Berthoz, 1997]

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ABBREVIATIONS

AC	anterior commisure
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APB	abductor pollicis brevis
ADM	abductor digiti minimi
BOLD	blood oxygen level dependent
CB	cerebellum
CMA	cingulate motor area
CMAP	compound muscle action potential
COM	center of mass
CST	corticospinal Tract
EEG	electroencephalography
EMG	electromyography
ERD	event-related desynchronization
ERP	vent-related potential
FMRI	functional magnetic resonance imaging
FOV	field of view
FWHM	full width at half maximum
HRF	haemodynamic response function
HWHM	half width at half maximum
GABA	gamma-aminobutyric acid
GLM	general linear model
EPSP	inhibitory post synaptic potential
IPSP	inhibitory post synaptic potential
ITI	inter-tap-interval
LFP	local field potential
LTD	long-term depression
LTP	long-term potentiation
M1	primary motor cortex
MEG	magnetoencephalography
MEP	motor evoked potential

MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartic acid
PC	posterior commisure
PET	positron emission tomography
PMC	premotor cortex
PMd	dorsal premotor cortex
PMv	ventral premotor cortex
ROI	region of interest
S1	primary somatosensory cortex
S2	secondary somatosensory cortex
SMA	supplementary motor area
SPM	statistical parametric mapping
RF	radio frequency
TE	echo time
TMS	transcranial magnetic stimulation
TR	repetition time
TRPD	task-related power decrease
TRPI	task-related power increase
V1	primary visual cortex

SUMMARY

The human motor system yields an enormous capacity for functional and structural reorganization. Many studies addressed this issue in the past by investigating plastic adaptation phenomena accompanying motor practice and motor skill acquisition. However, previous studies mainly used complex sequential movements and rather short training durations. The present thesis was therefore designed to address neural changes in human primary motor cortex (M1) function as induced by longer-term practice of simple repetitive finger tapping movements. During the course of training, which lasted for several weeks in each of the three studies, one single movement parameter, namely speed, was modified. The aim of the training was to increase maximum finger tapping frequency. There is much supporting evidence that M1 activity is strongly related to maximum tapping speed; however, longer-lasting practice of maximum speed tapping movements and associated effects on functional activation patterns in M1 have not yet been studied. Thus, all three experiments aimed to explore the following overarching question: Given that M1 has been suggested to operate at maximum processing capacity during maximum speed movements, how does it manage to "control" the higher maximum tapping speed that develops across training?

The three studies will be shortly summarized in the following:

Study 1: This study aimed to investigate changes in corticospinal excitability associated with longer training of elementary, maximum-speed tapping movements. All participating subjects were consistent right-handers and were trained using either the right or the left thumb. Transcranial Magnetic Stimulation (TMS) was applied to obtain motor evoked potentials (MEPs) from the abductor pollicis brevis (APB) muscle of the right and the left hand before and after training. As a result of training, a significant increase was observed in tapping speed accompanied by increased MEPs, recorded from the trained APB muscle, following contralateral M1 stimulation. In the case of subdominant hand training we additionally demonstrate increased MEP amplitudes evoked at the right APB (untrained hand) in the first training week. The results suggest that enhanced corticospinal excitability associ-

ated with practice of elementary movements may constitute a necessary precursor for inducing plastic changes within the motor system. The involvement of the ipsilateral left M1 likely reflects the predominant role of the left M1 in the general control (modification) of simple motor parameters in right-handed subjects.

Study 2 employed EEG to explore how M1 function changes to enable enhanced maximum movement rates induced by longer-lasting practice of tapping the left thumb at maximum speed. As in Study 1 all subject were consistent right-handers. Cortical function was assessed by recording task-related spectral EEG alpha power. LORETA was used to localize intracortical neuronal sources. The main result of this study is a decrease in neural activity in the dominant left hemisphere (ipsilateral to the trained hand) from pre- to posttraining whereas activity in the right hemisphere remained at a constant high level across training. This likely reflects the initially limited capacity of the right hemisphere to control effortful left-hand movements, but also highlights its ability to become more efficient in controlling such movements through training.

Study 3 uses fMRI to reinvestigate the arrangement of cortical finger representations in the human primary hand motor area and to specifically explore whether a 4-week-lasting elementary motor training changes this arrangement. As in the first two studies, the aim of the training was to increase maximum tapping speed with the subdominant thumb. First of all, the data indicate extensive overlap between finger-specific representations in M1, but nonetheless distinct centers of activation for movements of different fingers were identified. There was only weak evidence for a somatotopic organization of the five fingers in the homuncular sense, but strong support for an individual organization which is changed by training in an interesting manner: A) training reduced distances between finger representations and B) the smaller the distances between finger representations before training, the larger the training-induced speed gain. Results strongly suggest that a cortical organization that maximizes overlap and interlacing of neural tissue is favorable for selectively tapping a finger at maximum speed.

ZUSAMMENFASSUNG

Das motorische System des Menschen verfügt über eine enorme Kapazität zu funktioneller und struktureller Reorganisation. Die letzten Jahre motorischer Forschung haben gezeigt, dass dieses Potenzial eine der grundlegenden Voraussetzungen für motorisches Lernen darstellt.

Viele der bislang in diesem Bereich durchgeführten Studien haben ihren Fokus auf das kurzfristige Erlernen komplexer, sequentieller Bewegungen gelegt. Die vorliegende Arbeit hingegen konzentriert sich auf die neuronalen Veränderungen im primären motorischen Kortex (M1), die mit dem längerfristigen Training einer elementaren, repetitiven Finger-Tapping-Bewegung einhergehen. Das primäre Ziel des mehrwöchigen, intensiven Trainings bestand in der größtmöglichen Steigerung der maximalen Tapping-Geschwindigkeit. Es liegen bereits Studien vor, die einen Zusammenhang zwischen der Aktivität von M1 und der maximal Tapping-Geschwindkeit belegen. Das längerfristige Training maximal schneller Tapping-Bewegungen sowie die damit assoziierte Veränderung funktioneller Aktivierungsmuster in M1 wurden bisher jedoch nicht untersucht. Aus diesem Grund dienen die drei Experimente dieser Arbeit der Beantwortung der folgenden übergeordneten Fragestellung: Angenommen M1 beansprucht seine Verarbeitungsressourcen während maximal schnellen Tapping-Bewegungen maximal, wie bewältigt dieses Areal die trainingsinduzierte Erhöhung der maximalen Tapping-Geschwindigkeit?

Die drei Experimente werden im Folgenden kurz zusammengefasst:

Experiment 1 untersucht Veränderungen der kortiko-spinalen Erregbarkeit, die mit dem längerfristigen Training maximal schneller Tapping-Bewegungen einhergehen. Die Versuchspersonen waren konsistente Rechtshänder und führten das Training entweder mit dem rechten oder linken Daumen durch. Transkranielle Magnetstimulation (TMS) wurde angewandt um motorische Potenziale (MEPs) im *Musculus Abductor Pollicis Brevis* (APB) der rechten und linken Hand vor und nach dem Training zu evozieren. Als Ergebnis des Trainings wurde eine Steigerung der Tapping-Geschwindigkeit beobachtet, die mit einer Vergrößerung jener MEPs einherging, die nach kontralateraler TMS-Applikation vom trainierten APB abgeleitet wurden.

Zusätzlich zeigten sich im Fall des Trainings der subdominanten Hand vergrößerte MEP Amplituden auch am rechten (untrainierten) APB in der ersten Trainingswoche. Möglicherweise stellt diese mit dem Training assoziierte Erhöhung der kortiko-spinale Erregbarkeit eine notwendige Vorstufe für die Induktion funktioneller plastischer Veränderungen im motorischen System dar. Die erhöhte Erregbarkeit des ipsilateralen linken Motorkortex während des Trainings der linken Hand reflektiert dessen Überlegenheit hinsichtlich der generellen Kontrolle und Modulation einfacher motorischer Parameter bei rechtshändigen Versuchspersonen.

Experiment 2 verwendet EEG zur Untersuchung von Veränderungen des Aktivierungsmusters in M1, die mit der trainingsbedingten Steigerung der maximalen Tapping-Geschwindigkeit des linken Daumens einhergehen. Auch hier waren die Versuchspersonen rechtshändig. Die kortikale Aktivität wurde als aufgabenspezifische spektrale EEG-Aktivität im Alpha-Band erfasst. Zusätzlich wurde LORETA benutzt, um die entsprechenden intrakortikalen neuronalen Quellen zu lokalisieren. Hauptergebnis dieses Experiments ist die Verringerung der neuronalen Aktivität in der dominanten, linken Hemisphäre (ipsilateral zur trainierten Hand) im Verlauf des Trainings während die Aktivität in der rechten Hemisphäre nicht abnimmt. Dies widerspiegelt zum einen die anfänglich limitierte Kapazität der rechten Hemisphäre hinsichtlich der Kontrolle Bewegungen der linken Hand. Auf der anderen Seite deutet die Reduktion der Aktivität des linken M1 im Verlaufe des Trainings möglicherweise auf eine Steigerung der neuronalen Kontrolleffizienz des subdominanten, rechten Motorkortex hin.

Experiment 3 untersucht mittels fMRT die räumliche Anordnung der kortikalen Fingerrepräsentationen im primärmotorischen Handareal beim Menschen und exploriert ob sich diese Anordnung durch ein intensives finger-motorisches Training systematisch verändert. Wie in den beiden vorhergehenden Experimenten bestand das Ziel des Trainings in der Steigerung der maximalen Tapping-Geschwindigkeit des subdominanten linken Daumens. Obwohl die Daten generell extensive Überlappungen der fingerspezifischen Repräsentationen in M1 zeigen, konnten distinkte Aktivierungsmaxima für die Bewegung der einzelnen Finger identifiziert werden. Die räumliche Anordnung dieser Aktivierungsmaxima ist höchst individuell und verändert sich durch Training in einer interessanten Weise:

A) das Training reduziert die Distanzen zwischen den Fingerrepräsentationen und B) je kleiner die Distanzen zwischen den Repräsentationen vor dem Training desto größer ist der trainingsbedingte Zugewinn an Geschwindigkeit. Die Ergebnisse deuten darauf hin, dass eine kortikale Organisation, welche die Überlappung bzw. Verschmelzung funktioneller Areale maximiert, die Ausführung der maximal-schnellen Tapping-Bewegung eines einzelnen Fingers begünstigt.

S e c t i o n 1

NEUROPLASTICITY

A tremendous amount of research has been devoted to the issue of neural plasticity, particularly during the past two decades. Based on many interesting findings regarding functional and anatomical reorganization, we now know that plasticity is an intrinsic property of the neural system – the normal state of a system optimized to be continuously adapting to environmental pressures, experiences and physiologic changes. Reorganization can be observed at the level of behavior, anatomy, physiology, as well as on the level of cells and molecules. Plasticity constitutes the basic mechanism of development and learning – retained throughout lifespan. Plasticity in the sensorimotor system is the central topic of this thesis, addressed by all the three experiments. Besides reviewing some of the pioneering studies demonstrating neural plasticity, this section mainly focuses on anatomical and functional reorganization in the human sensorimotor system.

1.1 Neuroplasticity: A General Introduction

The term *plasticity* originates from the Latin word *plasticus*, which itself is derived from the Greek word *plastikos*, coming from *plastos,* which basically means 'molded'. Thus, to *be plastic* means to be capable of being shaped or formed, and capable of adapting to varying conditions. In a similar sense 'neuroplasticity' refers to the ability of the neural system to reorganize itself in response to internal and external events, like physiologic modifications or environmental changes and experiences. Plasticity therefore allows the nervous system to compensate for injury and disease but also to adjust its activity in response to new situations or to changes in its environment. Neuroplasticity may however also contribute to impairment. It has been suggested that focal dystonia and tinnitus are examples of maladaptive, functional reorganization leading to undesirable symptoms.

Nowadays, plasticity should be acknowledged as an intrinsic property of the nervous system *(for a review see Pascual-Leone et al., 2005)*. It is not only a state that is present to ensure development and growth in early childhood or to compensate for lesions and accompanying loss of function. Instead, it is the mandatory consequence of each motor act and action plan, of every sensory input, of each association and of positive and negative reinforcers. A dynamic two-way interaction becomes evident between changes in brain physiology and behavioral alteration. Behavioral alterations change physiology as changes in physiology change behavior. However, the exact relation between these two entities is still mostly unclear and certainly needs further exploration.

The concept of neuroplasticity and corresponding findings from basic research are of enormous relevance in the clinical setting. It is established that the organism can recover after a traumatic brain injury with the aim to restore normal levels of performance. Many examples of cortical and subcortical changes, modifications and adaptations of neuronal circuits in response to injury and manifold trainings have been provided in the past *(Liepert et al., 2004; Ramachandran, 2005)*.

1.2 Basic Principles of Plasticity: a Step into Neurophysiology

One of the essential and fundamental assumptions in cognitive neuroscience is that developmental changes, as well as learning and memory, are neurochemically based on the modifiability of the connection (synaptic) strength between at least two neurons in response to different stimuli or environmental cues. This mechanism is referred to as 'associative synaptic plasticity' and is considered to be an essential neural substrate of experience-dependent plasticity.

1.2.1 Synaptic plasticity: General mechanisms

The basic mechanism of synaptic plasticity is represented by the 'Hebbian rule'. Donald Hebb *(1949)* proposed:

> *"Let us assume that the persistence or repetition of a reverberatory activity (or "trace") tends to induce lasting cellular changes that add to its stabil-*

> *ity.… When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased…"* (in D.O. Hebb, The Organization of Behaviour: A neuropsychological theory. *New York: Wiley, 1949, p 62.*)

The simple idea behind it is the following: If neuron A stimulates a given neuron B repeatedly, then the connection strength between the two neurons will increase.

Two major mechanisms behind synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD), influence the degree to which activity in the presynaptic neuron leads to a depolarization of the postsynaptic neuron by influencing the efficiency of synapses between neurons.

1.2.1.1 Long-term potentiation

LTP is the long-lasting strengthening of the connection between two neurons. It was discovered in the mammalian hippocampus 40 years ago and has been a popular subject of research ever since *(for a review see Malenka & Bear, 2004)*. The process of LTP can be subdivided into two successive stages. The early stage (early-LTP) is protein-synthesis-independent and lasts up to several hours. To produce potentiation the process of early-LTP induces higher sensitivity of the postsynaptic side of the synapse to glutamate by appending additional AMPA receptors into the postsynaptic membrane.

To be more specific, early-LTP appears to strongly depend on calcium (Ca^{2+}) inflow into the postsynaptic cell. NMDA receptors would allow calcium inflow; however, they are normally blocked by magnesium (Mg^{2+}). In case of strong simultaneous input, the subsequent depolarization leads to the removal of Mg^{2+} allowing influx of Ca^{2+} ions that in turn activate calcium-dependent protein kinases. These kinases induce a series of mo-

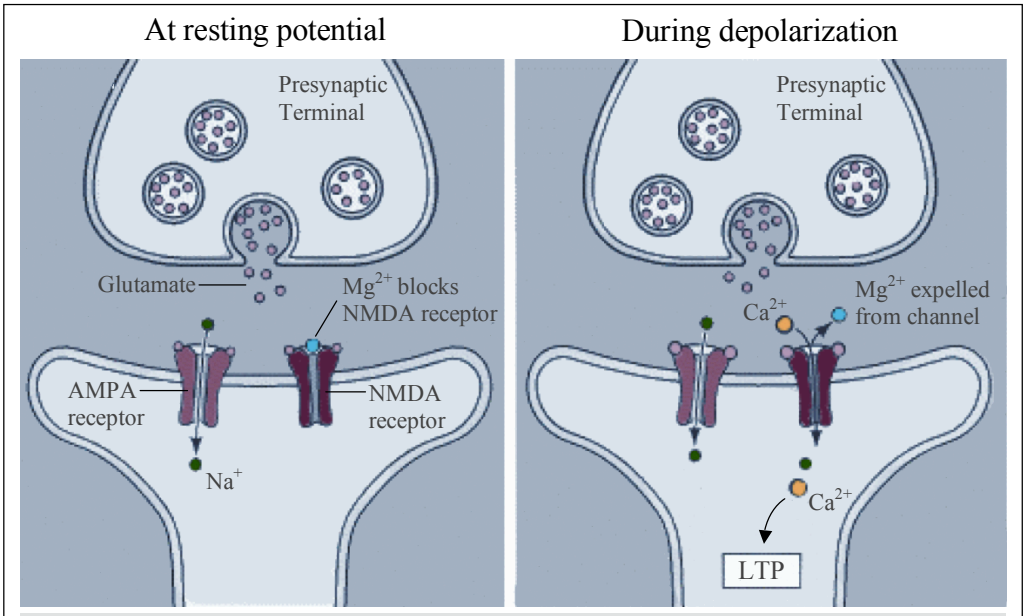


Figure 1.2-1: Mechanisms underlying LTP: The NMDA receptor channel can open only during depolarization of the postsynaptic neuron from its normal resting level. Depolarization expels Mg^{2+} from the NMDA channel, allowing current to flow into the postsynaptic cell. This leads to Ca^{2+} entry, which in turn triggers LTP. *(Figure taken from Purves et al., 2001)*

lecular changes that contribute to an enhanced sensitivity of the receptor channel complex to glutamate; therefore boosting responses to subsequent input (see Figure 1.2-1). Importantly, both, pre- and postsynaptic activation is required for the process of LTP to occur. In the second phase (late-LTP), which lasts from days to months, there is a pronounced strengthening of the postsynaptic response mainly due to the synthesis of new proteins. These proteins include glutamate receptors, and structural proteins that enhance existing synapses and, therefore, contribute to form new connections. There is now evidence that LTP triggers the synthesis of retrograde messengers that diffuse back into the presynaptic neuron and aim to increase the probability of neurotransmitter vesicle release in response to subsequent stimuli. However, more experimental evidence for late-LTP is needed *(Malenka & Bear, 2004; Munakata & Pfaffly, 2004)*.

1.2.1.2 Long-term depression (LTD)

In contrast to LTP, LTD refers to the weakening of a synapse and therefore to a reduction in connection strength between two neurons. LTD is

of great importance in order to enable bi-directional modification of synaptic efficiency and shares several key features with LTP. LTD also depends on the activation of NMDA receptors and on the resulting influx of Ca^{2+} into the postsynaptic cell. Although not sufficiently explored yet, the postsynaptic amount of Ca^{2+} appears to be one of the major determinants of whether LTP or LTD is induced. When the Ca^{2+} influx is below a particular threshold, LTD occurs; when the threshold is exceeded, LTP occurs. The process of LTD is suggested to reflect a lack of coordinated activity between pre- and postsynaptic element *(Gaiarsa et al., 2002; Malenka & Bear, 2004; Munakata & Pfaffly, 2004)*.

1.2.2 Synaptic plasticity in the primary motor cortex

Based on the discussion of basic mechanisms of plasticity, such as LTP or LTD, the focus is now being placed on particular mechanisms underlying use-dependent plasticity in the primary motor cortex. As discussed in detail by Sanes & Donoghue *(2000)* a "candidate substrate for primary motor cortex (M1) plasticity is the system of horizontal connections that span M1". This network of connectivity is used to functionally couple groups of M1 neurons with the aim to built dynamic motor maps. Reorganization within M1 may be substantially based on synaptic plasticity of these horizontal fibers.

It has been well established that activity-dependent modification of neural pathways by LTP and LTD, extensively proven for the hippocampus, also plays an important role in motor cortex plasticity. Particularly, it was shown that horizontal connections have the capacity for long-term synaptic changes *(Hess & Donoghue, 1994; Aroniadou & Keller, 1995),* thus, supporting the above-mentioned hypothesized role of the horizontal fiber network in serving functional reorganization. In analogy to the early studies that showed synaptic plasticity in the hippocampus, the strength of horizontal connections can be up-regulated by LTP and down-regulated by LTD, induced respectively by high- and low-frequency stimulation. There is evidence that this ability for modification of synaptic efficiency is retained throughout life. Interestingly, however, whereas LTD can readily be provoked in matured M1, the induction

LTD can readily be provoked in matured M1, the induction of LTP appears to be subject to constraints *(for a review see Sanes & Donoghue, 2000)*.

In conclusion, structural and functional characteristics of the primary motor cortex support and emphasize its tremendous capability for functional reorganization and enable the dynamic adaptation to changing environmental requirements. The horizontal connections represent the anatomical substrate for reorganization, while the proven sensitivity of those connections for LTP / LTD provides the corresponding mechanism.

1.2.3 Axonal sprouting and neurogenesis

On the molecular and cell level, structural changes extent beyond alterations in synaptic efficiency and synapse formation to changes in spine density and dendritic length. In case of a degenerating axon, adjacent healthy axons sprout into the deserted territory left by the degenerated tissue and form new synaptic contacts. This collateral sprouting is activated by degenerating tissue *(Pinel, 2001)* and therefore keeps the cortical tissue functioning throughout neural cell loss. Furthermore, recent intriguing studies in the field of neurobiology have provided convincing evidence that neurogenesis (the formation of new nerve cells) is possible in the adult, mammalian brain. There is much evidence from previous animal studies that the improvement of learning performance in rats in a rich, complex environment is accompanied by a higher number of synapses per neuron and further by thicker cortices compared to rats raised in isolated, poor environments *(van Praag et al., 1999; 2000; 2005)*. Furthermore, growing up in such rich complex environments leads to higher levels of neurotrophin-3 (NT-3) mRNA and, thus, to the growth of new dendritic spines in the hippocampus and visual cortex of rats *(Torasdotter et al., 1996)*. In addition, a complex stimulating environment appears to promote neurogenesis in the dentate gyrus of the adult mouse hippocampus *(Kempermann et al., 1998)*.

In humans, with particular respect to cognitive development in children, a comparable effect of enriched environments is claimed, though experimental evidence still has to be provided. A higher educational level has been proposed

to go along with a reduced risk to suffer from dementia (Alzheimer and Parkinson-related dementia) – an important finding that also supports the beneficial influence of stimulating environments on cerebral health *(Mortel et al., 1995; McDowell et al., 2007)*.

1.3 The Step from Synapses to Representational Maps

It was pointed out in the previous sections that learning across lifespan is based on the modification of connectivity between neurons by means of assigning different weights to the synaptic junction and even by means of morphological changes through neuro- and spinogenesis. Taking a more macroscopic perspective, cortical organization is often described in terms of maps (e.g., retinotopic and tonotopic maps, as well as sensory and motor maps). More than two decades of research have shown that these maps are not 'hard-wired' but instead undergo plastic changes in response to peripheral manipulations, environmental pressures and behavioral experience throughout life. Within certain limits, the cortex can reallocate cortical area in a use-dependent manner.

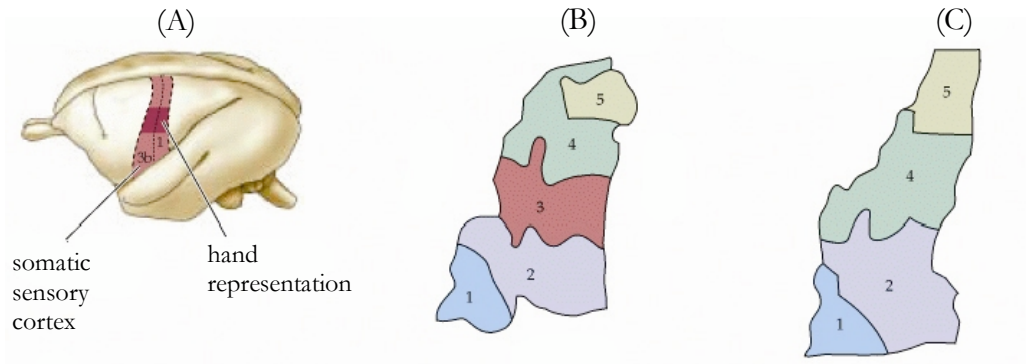


Figure 1.3-1: Functional reorganization in the somatosensory cortex of an owl monkey following amputation of a digit (data from Merzenich et al. 1984). (A) Location of the sensory hand representation. (B) Arrangement of finger-specific representations before amputation [numbers correspond to different digits]. (C) Reorganized map of the hand representation two months after amputation of digit 3 (after Merzenich et al., 1984). *[Figure modified from Purves et al., 2001]*

Synaptic plasticity as a functional characteristic of the cortex has been intimately linked to cortical map plasticity by providing some evidence that synaptic and cellular mechanisms such as LTP and LTD underlie this form of representa-

tional plasticity *(for a review see Buonomano & Merzenich, 1998)*. At the cortical level synaptic plasticity refers to the detection of temporally correlated inputs. The rational behind it can be illustrated using the example of topographic somatosensory representations; peripheral inputs that fire in close temporal proximity are more likely to represent adjacent areas on the peripheral sensory sheets *(Merzenich et al., 1996)*.

The early work of Merzenich et al. *(1984)*, and many other research groups, has revealed the seminal finding that, in monkeys, somatosensory cortical maps change after manipulations of peripheral inputs (e.g., sensory nerve transection, amputation). Deafferentation does not result in a permanent unresponsiveness of the affected cortical area, but instead it evokes a tremendous reorganization of the somatotopic map. When existing cortical representations are prevented from receiving sensory input from the corresponding body part, representations of neighboring body parts will take over the non-functional cortical territory. This mechanism of reorganization has been explained by unmasking of existing though previously suppressed horizontal connections or thalamo-cortical inputs. Similar effects occurred with changes in sensory experience, for instance following an artificially produced digit syndactyly in monkeys. Several months after digit fusion, cortical mapping revealed that somatotopic borders between the fused digits had disappeared resulting in double digit receptive fields of many cortical units *(Allard et al., 1991)*.

To link the underlying map organization of the cortex and functionality within these mapped representations, it has been suggested viewing sensory and motor maps as sort of scaffold upon which highly dynamic functional representations are built by a mixture of both, *bottom-up* and *top-down* inputs. Modifications or tuning of functionality within these scaffolds seem to reflect short- and medium-term plastic effects, while plastic changes of the scaffolds themselves might rather be a sign of medium- to long-term plastic effects *(Elbert & Rockstroh, 2004)*. There are several conditions leading to changes of cortical maps:

(1) Reorganization of cortical maps by deprivation: Plasticity can be induced by cortical deprivation or deafferentation. The accompanying

disuse leads to an invasion of neighboring cortical regions into the non-functional territory.

(2) Reorganization of cortical maps after lesions: Plasticity can be induced by cortical lesions in order to restore function.

(3) Experience-(use-)dependent reorganization of cortical maps: Plasticity can be induced by increased sensory input or motor output in the context of training or experience. Generally, intensive training or experience leads to an expansion of cortical representations (new space is recruited). Furthermore, synchronous inputs (or outputs) lead to the fusion of corresponding cortical representations, whereas asynchronous inputs lead to an enhanced segregation of associated cortical zones.

1.4 Representational (Map) Plasticity in Humans

Following the seminal work of Jenkins et al. *(1990)* and Recanzone et al. *(1992)* in monkeys, phenomena of sensory map reorganization following injury or training were also revealed in humans.

For instance, Pascual-Leone & Torres *(1993)* studied changes in the hand representations of adults who had learned to 'read' Braille. They demonstrated larger cortical representations for the right index finger (which was involved in 'reading') as compared to the left index finger or the right index finger of non-Braille 'readers'. Furthermore, Elbert et al. *(1995)* showed increased somatosensory representations of the left hand in professional violin players compared to non-musician controls. In addition, enlarged auditory networks in musicians have been reported *(Pantev et al., 2003)*.

Evidence for the 'invasion' of non-used, input-deprived cortical territory in humans (e.g., after deafferentation) has been provided by Elbert et al. *(1994, 1997)* for the somatosensory cortex. Extensive reorganizations within the somatosensory cortex after injury have been discussed as potential cause of phantom pain *(Flor et al., 1995)*. Among the most prominent examples of functional reorgani-

zation following lesions in the human brain is the cross-modal use of occipital cortex in blind individuals. Following the observation of crossmodal plasticity in visually deprived cats *(for an overview see Rauschecker, 1995)*, Weeks et al. *(2000)* revealed the involvement of the human occipital cortex during sound localization, a function blind subjects show superior performance at *(Lessard et al., 1998; Weeks et al., 2000)*. Sadato et al. *(1996)* were the first to show activity in the occipital cortex of blind subjects during Braille reading. In addition, Cohen et al. *(1997)* and subsequent studies by Pascual-Leone et al. *(2000)* and Walsh & Pascual-Leone *(2003)* have proven that disruptive TMS pulses applied to the occipital cortex disturbed Braille reading performance in blind but not control subjects. Several further studies have examined crossmodal plasticity in blind subjects, specifically aiming to investigate visual imagery, differences between early and late blind individuals, or the neural processing of linguistic tasks *(for review see Merabet et al., 2005)*. Very recent, striking studies have shown that complete visual deprivation in sighted subjects (blindfolded for 5 days) is already sufficient to evoke crossmodal plastic changes, meaning that the occipital cortex is getting involved in auditory and tactile information processing *(Pascual-Leone, 2001; Pascual-Leone et al., 2005)*. Given the short time-scale of changes, it seems highly unlikely to attribute them to the built-up of new connections. Therefore, there must be preexisting connections between somatosensory/auditory and visual areas that are rapidly unmasked following visual deprivation. Indeed, such connections have been found *(Falchier et al., 2002; Rockland & Ojima, 2003)*. However, while such changes are rather transient in nature, it is likely that enduring changes in the neural system including the establishment of new neuronal connections occur following early sight loss.

Meanwhile an impressive amount of findings with respect to neuroplasticity has been published, addressing both short- and long-term reorganization after lesions and after the application of manifold trainings. Unfortunately, there is no agreement on standardized definitions of what is considered to be short-term and long-term. As for studies assessing training-related neural changes, that provide the most relevant theoretical background for this thesis, the following classification scheme will be used in the upcoming sections:

i. Short-term training: refers to training durations of less than a day (often limited to one training session).

ii. Medium-term training: includes trainings with more than one training session (up to several weeks) – the experimental studies included in this thesis can be considered belonging to the category of medium-term training.

iii. Long-term training: refers primarily to several years of trainings, as it is the case in professional musicians or athletes.

The main focus of all experiments accomplished in the framework of this thesis is specifically placed on training-related plasticity in the human sensorimotor system. The discussion of earlier studies in the field of human neuroplasticity will therefore be limited to relevant domain-specific findings. There are mainly two approaches to study training-related changes in the sensorimotor system. The first would be the investigation of naïve subjects before and after a particular motor training. This is consistent with a *longitudinal* study design in which the same group of subjects is evaluated at several consecutive time points. Secondly, a *cross-sectional* study design would compare two groups, representing different populations (e.g. professional vs. naïve subjects).

There is a large amount of research (both, longitudinal and cross-sectional studies) on neural changes accompanying (mostly) short-term motor skill learning. Corresponding findings will be presented and discussed in ▸Section 3.2 in the context of functional properties of the sensorimotor system with respect to movement control. Long-term motor training will be addressed in the next section by discussing neuroplasticity in the unique population of professional musicians. Musicians, but also experts in other domains (e.g., athletes), have been proven to be ideal subjects to study effects of life-long training.

1.4.1 The 'professional' brain as a model of neuronal plasticity

Performing music on a professional level is undoubtedly among the most complex motor acts, placing extreme neural control demands primarily onto neural

motor and auditory systems. A pianist for instance is capable of controlling the bimanual production of up to 1.800 notes per minute *(Munte et al., 2002)*.

Due to the extraordinary amount of life-long motor training, professional musicians constitute an ideal population for studying long-term plasticity within the sensorimotor and auditory system *(Schlaug, 2001; Munte et al., 2002; Jäncke, 2002)*. Given the focus of the present thesis, the reported findings in this section mainly focus on the sensorimotor system. Several anatomical and neurophysiologic peculiarities have been reported in association with the development of exceptional fine motor skills. Recent fMRI studies, for instance, have revealed unusual cortical activation patterns during music-related uni- or bimanual movements in highly skilled pianists and string players as compared to non-musicians *(Krings et al., 2000; Jäncke et al., 2000c; Lotze et al., 2003b)*. In general, musicians show weaker hemodynamic responses within the motor system, including the primary motor area (M1), the premotor cortex (PMC), and the mesial motor wall (presupplementary motor area: pre-SMA, posterior part of the supplementary motor area: SMA proper, cingulate motor area: CMA), suggesting a more efficient way to control these movements. There is additional evidence for a larger efficiency of movement control by the cerebellum of musicians compared to non-musicians *(Koeneke et al., 2004)*. Furthermore, it was shown that learning new motor paradigms is not only easier for musicians but is also accompanied by weaker hemodynamic responses than those seen in non-musicians. A very recent study demonstrated stronger involvement of audio-motor integration areas (especially in the dorsal premotor cortex, PMd) in musicians compared to non-musicians while either playing music without acoustic feedback or listening to music without playing *(Baumann et al., 2006)*.

Another line of research has revealed substantial differences in musicians with respect to macroanatomical measures of brain areas which are involved in musical training. Professional right-handed piano players, for instance, have been shown to have enlarged cortical hand motor regions compared to non-musicians. The between-group difference is more pronounced for the subdominant motor cortex *(Amunts et al., 1997)*, resulting in reduced between-hemisphere asymmetries for the group of musicians. Further studies found

larger anterior parts of the corpus callosum in professional pianists, indicating enhanced interaction between the motor areas of the two hemispheres *(Schlaug et al., 1995; Lee et al., 2003)*, which is thought to be related to the excellent ability of pianists to integrate the action of both hands. An important finding is the correlation of the anatomical changes with the age at which musical training commenced, suggesting that use-dependent stimulation is the main aspect determining these anatomical peculiarities *(Schlaug et al., 1995; Amunts et al., 1997)*. A recent elegant study using voxel-based morphometry to detect structural differences between pianists and non-musicians across the whole brain found larger grey matter volumes in the motor network of the musician group including M1, the somatosensory areas (S1), PMC, and the left cerebellum (CB) *(Gaser & Schlaug, 2003)*. Another recent study found a significant difference in absolute and relative cerebellar volume between male musicians and non-musicians *(Hutchinson et al., 2003)*.

1.5 Maladaptive Plasticity

The characteristic of the nervous system of being plastic and, thus, of being highly capable of change, certainly harbors the risk of changes that may lead to unwanted behavioral consequences. To provide an adequate example for the 'dark side' of neuroplasticity, I get back to the musician model. The clinical picture of (focal) dystonia, which literally means *abnormal muscle tone*, can be described as a neurological movement disorder characterized by involuntary, sustained muscle contractions that lead to twisting movements or abnormal posture. It has been argued that the excessive musical motor training may lead to an unwanted change in the cortical arrangement of functional motor and sensory representations. Several recent studies have assessed sensorimotor excitability in patients suffering from focal dystonia (dystonic symptoms are confined to particular muscles or muscle groups). The main result is an abnormal responsiveness of the sensorimotor cortex in the group of patients *(Playford et al., 1998; Quartarone et al., 2003; Siebner et al., 2003)* as well as changes in the arrangement of somatosensory and motor cortical finger representations *(Byl et al., 1996; Elbert et al., 1998; Pascual-Leone, 2001)*. In a recent study, Quartarone et al. *(2005)*

have demonstrated impaired homeostatic plasticity mechanisms in dystonic patients. There is evidence that normally the positive-feedback nature of LTP is compensated for by a dependence of the amount of LTP on the level of activity in the postsynaptic neuron. In other words, the greater the ongoing activity, the less effective are processes leading to LTP, whilst processes leading to long-term depression (LTD) are enhanced. Impairments in homeostatic plasticity may therefore trigger an excessive increase in synaptic effectiveness, which might contribute to generate dystonic symptoms.

Several therapy approaches have been considered and tested in order to induce new changes to compensate for the consequences of maladaptive cortical reorganization. They include both, behavioral motor trainings (constraint-induced therapy approaches) as well as direct methods to modify neuronal firing rates and, thus, cortical excitability. Unfortunately, up to now, there is no established causal therapy for focal hand dystonia.

1.6 Summary

Research over the past 20 years has established that cortical maps in the adult brain are not fixed, but change dynamically. The cortex is able, throughout lifespan, to re-assign cortical areas to represent the selected peripheral inputs or, in case of the motor domain, to reflect the efferent demand. However, the fundamental idea is the same: Plasticity is the normal ongoing state of the neural system across life; it is a consequence of every neural activity in response to internal physiologic events and external environmental stimulation and needs. Therefore, by definition, plasticity can at the same time be a mechanism causing pathology.

Despite the substantial advances in understanding some of the basic (molecular and cellular) principles of plasticity, we do not yet have a sufficient understanding of the relation between changes at the neural and at the behavioral level. The challenge of future research in that field is to further explore plastic mechanisms, but especially, and necessarily, to address the relation between neural activity and behavior. The clinical aim is to exploit and to benefit from the neuronal feature of plasticity by *manipulating* functional activation patterns - by suppressing reorganization processes that lead to unwanted behavior and by boosting those changes that result in a positive behavioral outcome for the individual.

Section 2

ANATOMY OF THE MOTOR SYSTEM

A major aim of this thesis is to investigate reorganization processes within the cortical sensorimotor system that accompany motor practice. This section provides an overview of the anatomy and key organization principles of the human motor and sensorimotor systems. Particular attention is paid to the primary motor cortex (M1) since this area is focused by all experiments of this thesis. For the purpose of introduction, Figure 2.1-1 illustrates the main constituent parts of the human motor system.

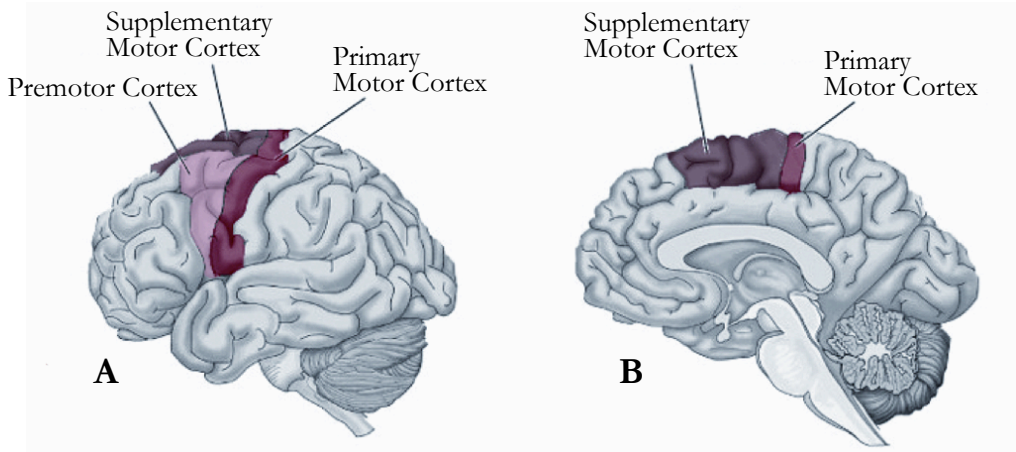


Figure 2.1-1: Lateral (A) and medial (B) views on the human brain showing main components of the human motor system *(modified from Purves et al., 2001)*

2.1 The Motor System: An Introduction

There has been a wealth of studies during the past century considerably advancing the knowledge of structural and functional properties of the motor system. Based on recent histological, physiological and anatomical findings, the structure of long-established cortical and subcortical motor areas has been adjusted to account for the emergence of functionally and microanatomically distinct sub-areas. Particular advances have been made in understanding anatomical and

functional connectivity in the widely distributed motor network, thus providing insights in the way it accomplishes skilled motor behavior and skill learning.

2.1.1 Discovering the motor cortex: A short historical recollection

Employing galvanic stimulation to a dog's brain, Gustav Theodor Fritsch and Eduard Hitzig *(1870)* were the first to show that circumscribed cortical areas are involved in movements of the contralateral limbs. Corroborating this result, they further demonstrated weakness in these limbs after the ablation of corresponding areas. At about the same time, John Hughlings Jackson observed that abnormal movements during epileptic seizures migrate systematically from one part of the body to another, therefore he suggested an organized map of the body's musculature within the motor cortex *(Jackson, 1863)*. Several decades later, Charles Sherrington reported evidence for rough motor maps in the motor cortex of great apes using electrical stimulation techniques *(Leyton & Sherrington, 1917)*. In the 1930s, deeply influenced by Sherrington's experiments, the Canadian neurosurgeon Wilder Penfield made the seminal discovery that stimulation of Brodmann's area 4 readily elicited localized muscle twitches, and thus extended Sherrington's findings to the human brain *(Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950)*.

2.1.2 How many motor regions are in the brain?

Besides the primary motor cortex (M1) which has been the main subject of early electrical stimulation experiments, a group of secondary motor areas necessarily contribute to the planning, adaptation and execution of movements. The number of existing motor areas is still a matter of debate. It seems that the heterogeneity of motor regions increases from decade to decade with the development of new and better micro- and macroanalytic techniques *(Picard & Strick, 1996; Roland & Zilles, 1996)*. While in the beginning a distinction was made only between Brodmann areas 4 and 6, laterally and medially (as depicted in Figure 2.1-1), a much more complex pattern with around ten areas has emerged up to now. Problems already arise when trying to set up criteria for defining a motor area *(Roland & Zilles, 1996)*. So far, motor sub-regions have been mainly defined on the basis of electrophysiological evidence and anatomical inter-connections.

However, most sophisticated cyto- and receptor-architectonic analyses are now adopted to re-evaluate cortical motor areas. A common parcellation is reflected by (a) the division of the primary motor cortex into areas 4a and 4p *(Geyer et al., 1996)*, (b) the division of medial premotor cortex into pre-SMA and SMA proper *(Zilles et al., 1995)*, (c) the division of the lateral premotor cortex into a dorsal (PMd) and a ventral (PMv) sub-region with PMd being again subdivided into a rostral (PMdr) and a caudal part (PMdc) *(Barbas & Pandya, 1987)* and finally (d) the division of cingulate cortex into the rostral (RCZ) and caudal (CCZ) cingulate zones whereat RCZ is further divided into an anterior and a posterior portion *(Picard & Strick, 1996)*. Experimental, anatomical and histological evidence for the proposed parcellation is provided below.

2.2 The Primary Motor Cortex

M1 works in association with premotor areas to plan and execute movements. Cells of motor cortex layer V send long axons down the spinal cord to synapse directly onto alpha motor neurons which connect to the muscles. Lesions of the precentral gyrus result in paralysis of the contralateral side of the body.

2.2.1 Microstructure and localization

The early experiments of Penfield have provided first insights into structural and functional characteristics of the motor cortex and the downstream corticospinal tract (CST). Both, premotor and motor cortex are characterized by agranular cytoarchitectonic pattern in cortical layers II and IV. In contrast to area 6 (premotor cortex), gradually adjoining area 4 (M1) is featured by the high density of large Betz cells (cell body size can be up to 100 micrometers in diameter) in the cortical output layer V whose axons account for about 3 – 5 % of the CST. The remainder consists of axons originating from pyramidal neurons *(Schieber & Hibbard, 1993; Zilles et al., 1995; Roland & Zilles, 1996)*. M1 is bordered caudally by the highly granular somatosensory cortex and inferiorly by the Sylvian fissure. Medially, it is contiguous with the paracentral lobule. The cytoarchitectonic map of Brodmann illustrates the traditional view of M1 as one homogeneously organized area. However, recent work based on detailed cyto-

and receptor-architectonic analysis proposes the distinction of an anterior (area 4a) and a posterior (area 4p) sub-area within area 4 *(Zilles et al., 1995; Geyer et al., 1996; Zilles, 1996)*. Although brain imaging studies have demonstrated separate representations for some fingers in the two sub-areas, clear experimental evidence for a functional relevance of this distinction is still missing.

2.2.2 The question of somatotopy

The fundamental concept of somatotopy – generally referring to the organized correspondence between a cortical region and the body – has evolved from the early electrical cortical stimulation experiments in animals and humans *(Fritsch & Hitzig, 1870; Penfield & Boldrey, 1937; Woolsey et al., 1952)*. More than a century later, we now know that somatotopy represents a key principle of primary motor cortex (M1) organization and is well established for the functional organization of major body parts. In contrast, the existence or non-existence of a fine-scale somatotopic arrangement within M1 subareas has been an issue of controversial debate during the last decade. Most work conducted to answer the question of fine-scale somatotopy has focused on the arrangement of functional finger representations in the M1 hand area. Discussing the issue of motor cortex somatotopy is intrinsically tied to the schematic homuncular figure *(Penfield & Rasmussen, 1950; Woolsey et al., 1952)*, thus, raising the question of unintended somatotopic detail *(Schott, 1993; Indovina & Sanes, 2001)*. Given that known organization principles as convergence and divergence on a cellular level and the phenomenon of sharing neural substrate are not as easy qualified for illustration, Woolsey et al. (1952) themselves cautioned:

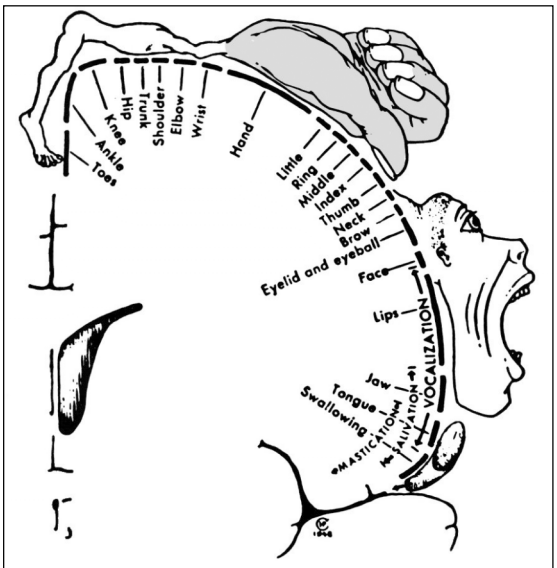


Figure 2.2-1: The motor homunculus

> *"It must be emphasized, however, that this diagram is an inadequate representation of the localization pattern since in a line drawing one cannot indicate the successive overlap which is so characteristic a feature of cortical representation."* (Woolsey et al. 1952, pp. 251-252)

Despite that cautions, the idea of an orderly body map has been the starting point of many investigations aiming to assess fine-scale finger somatotopy in M1. Several of the previous studies were indeed able to provide evidence in favor of a somatotopic gradient within the M1 hand area *(Kleinschmidt et al., 1997; Lotze et al., 2000; Beisteiner et al., 2001; Hlustik et al., 2001; Dechent & Frahm, 2003; Beisteiner et al., 2004)*. Other studies however failed to demonstrate somatotopic organization at the level of finger representations *(Schieber & Hibbard, 1993; Sanes et al., 1995; Schieber & Poliakov, 1998; Volkmann et al., 1998)*. The common denominator of past studies – regardless of whether fine-scale somatotopy has been reported or not – is the observation of extensive overlap between single finger representations. Patches of activity associated with the movement of one finger have been reported being distributed throughout the entire M1 hand area. For a more detailed survey of the current literature that issues somatotopy, the interested reader is referred to the introduction and discussion sections of the corresponding publication (▸Section 8).

It has been shown before, that the arrangement of finger representations is sensitive for effects of neural plasticity. Long-term training of violin playing has been related to larger distances between finger-specific somatosensory representations *(Elbert et al., 1995)*. Further evidence comes from a study by Volkmann et al. *(1998)* reporting larger distances between dipole sources for different hand movements in the dominant M1. Training-related changes in the arrangement of cortical finger representations in M1 have not been directly reported yet.

2.2.3 Afferent input

The primary motor cortex receives strong projections from the ventral lateral nucleus of the thalamus (VL/VA). Many studies provide data suggesting that the thalamus receives and integrates inputs from the basal ganglia and the cere-

bellum. By means of these indirect connections subcortical parts of the motor system do participate in the fine-tuning and coordination of motor commands. Cortical afferences mainly originate in the lateral and mesial premotor cortices. Thirdly, major input reaches M1 from the parietal cortex, including direct projections from the primary and secondary somatosensory cortices *(Kandel et al., 2000)*. Information regarding anatomical connectivity comes almost exclusively from studies in non-human primates. So far there is only little direct evidence for the validity of transferring findings from primate to the human brain. However, the relatively new method of Diffusion Tensor Imaging (DTI) and accompanying fiber tracking algorithms have been proven to be suited to non-invasively quantify fiber bundles in the living human subject and thus, might contribute to this issue in the near future.

2.2.4 Efferent output: The corticospinal tract

The corticospinal tract (CST) is the largest descending motor pathway and originates mainly from the pyramidal cells in the cortex of each cerebral hemisphere (other cortical areas contribute as well, e.g. the primary somatosensory cortex). Once the axons leave the pyramidal cells, they enter the white matter and course through the internal capsule. Within the internal capsule, sensory information travels up on the way from the thalamus to the cortex, and motor information travels down to the spinal cord. On its way down, the

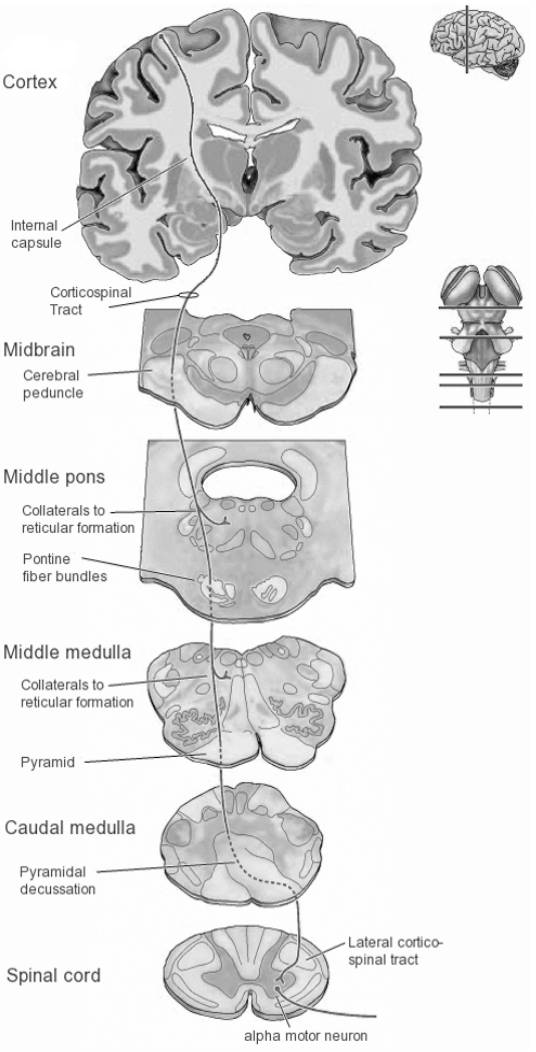


Figure 2.2-2: The corticospinal tract *(modified from Purves et al., 2001)*

CST passes through the cerebral peduncles at midbrain level. Cortico-pontine axons that have been part of the CST until here leave the fiber bundle to transmit information to pons and cerebellum. The remaining corticospinal axons process through the medullary pyramids. At the very caudal-most end of the medulla approximately 80% of the fibers from each hemisphere cross (pyramidal decussation) and continue to descend in rough somatotopically ordered fashion in the lateral column of the opposite side. The other 20% continue down ipsilaterally to innervate the medially located motor neurons targeting axial and proximal muscles bilaterally *(Kandel et al., 2000)*. Then, the crossed motor fibers approach the grey matter of the spinal cord at their target levels. Once in the ventral horn the fibers synapse either on interneurons or directly on the α-motor neurons, preferentially innervating the limbs and distal muscles.

2.3 Non-primary Cortical Motor Areas

2.3.1 Premotor cortex (PMC)

Neurons in the premotor cortex influence motor behavior indirectly through extensive reciprocal connections with M1 and directly via pyramidal and extrapyramidal fibers, influencing motor neurons of the brainstem and spinal cord. A major efference originating in the PMC projects via Pons to the Cerebellum, which in turn influences M1 through the thalamus (fronto-pontine loop). In the macaque monkey, the territory of PMC has been functionally subdivided into a dorsal (PMd) and a ventral part (PMv), each consisting of caudal and rostral sub-zones *(for an overview see Rizzolatti et al., 1998)*. As aforementioned, the question of homology between human and monkey premotor areas is in dispute, particularly when considering the enormous differences in PMC volume. So far, corresponding studies in humans were not able to sufficiently assign distinct functions to the PMC sub-regions. The validation of anatomical fractionation by means of functional data remains therefore an issue of future research. In general, past studies indicate the involvement of PMC areas in higher motor functions that precede the actual motor execution. More specifically, the PMC is supposed to use information from other cortical regions to select movements

appropriate to the action context *(Kawashima et al., 1994; Grafton et al., 1996; Grafton et al., 1998)*.

2.3.2 Supplementary motor area (SMA)

The SMA, like the PMC, is intimately involved in selecting a specific movement (or movement sequence) from the repertoire of possible movements. However, the SMA seems to be specialized for preparing movements specified by internal rather than external cues *(Okano & Tanji, 1987; Halsband et al., 1994)*. Based on physiological and histological findings, the classical SMA has been subdivided into two different sub-regions *(Zilles et al., 1996)*. The posterior SMA proper is more closely connected with M1 and maintains direct connections with the spinal cord, while the pre-SMA is more strongly connected with the prefrontal association cortex (PFC). This difference in connectivity indicates clear functional consequences with pre-SMA motor function being more abstract compared to that of SMA proper *(Picard & Strick, 1996)*. The border between the two SMA sub-regions corresponds roughly to the Y-position of the anterior commissure. Recent studies using Diffusion Tensor Imaging (DTI) provide further evidence for this distinction by revealing an abrupt change of the connectivity profile where the border between supplementary motor area (SMA) and pre-SMA is expected *(Johansen-Berg et al., 2004)*.

2.3.3 Cingulate motor area (CMA)

The three distinguishable cingulate motor areas in the monkey brain (rostral CMAr, ventral CMAv, and dorsal CMAd) are located in the depth of the cingulate sulcus *(Picard & Strick, 1996)*. Without going too much into detail, it has generally been shown, that these sub-areas are profoundly different with respect to their afferent and efferent connections. While CMAv and CMAd maintain connections with M1, CMAr is rather connected to the prefrontal cortex (PFC). Microstimulation experiments have provided further support by demonstrating only a weak impact of the CMAr onto the spinal cord. In the human brain another terminology has been proposed dividing the cingulate cortex into a rostral (RCZ) and a caudal cingulate zone (CCZ) whereat the RCZ is further divided into an anterior and a posterior portion. Homologies between monkey and hu-

man cingulate sub-regions have been hypothesized, but not yet conclusively proven. Some functional differences have been tied to the underlying structural disparity by assigning RZC activation to more complex and CCZ activation to rather simple movements.

2.4 Subcortical Motor Systems

Given that subcortical parts of the motor system are not directly in the focus of the thesis, this sub-section will place particular interest onto the neural loops interconnecting these structures with the motor cortex via thalamic relay nuclei.

2.4.1 Cortex - Striatum - Pallidum - Thalamus - Motor Cortex

Cortical fibers originating in various cortical regions (mostly motor and prefrontal, but also parietal brain regions) converge on the basal ganglia (BG), which in

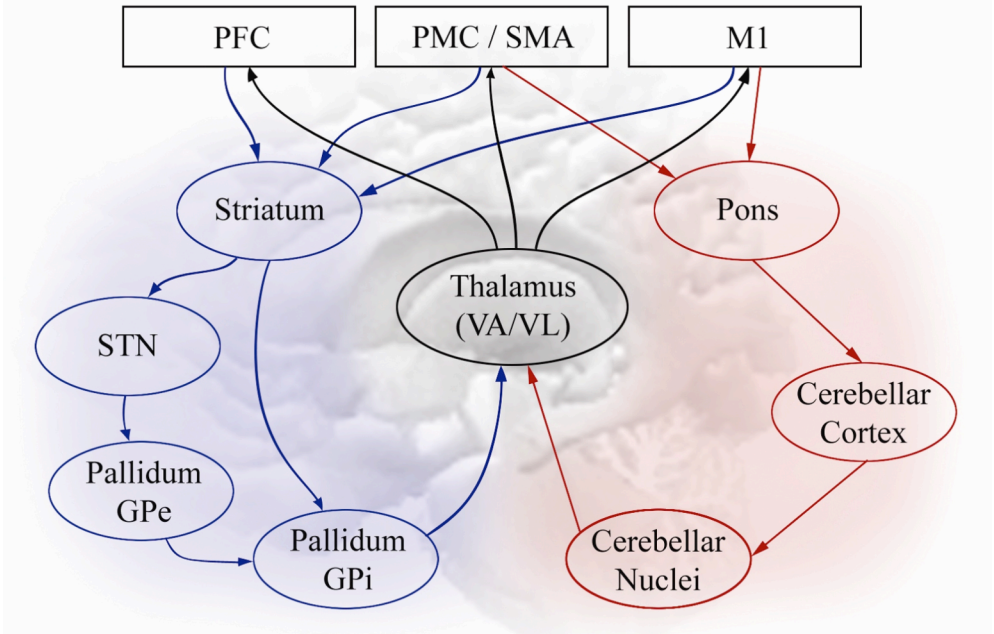


Figure 2.4-1: Schema of the major connection loops between subcortical (basal ganglia, cerebellum) and cortical motor areas. The thalamus acts to relay information from subcortical to cortical motor areas. Information from the basal ganglia is relayed via VA, and information from the cerebellum is relayed via VL. [GPi = globus pallidus, pars interna; GPi = globus pallidus, pars externa; STN = subthalamic nucleus; PFC = prefrontal cortex, PMC = premotor cortex, SMA = supplementary motor area; M1 = primary motor cortex, VA=ventral anterior nucleus of the thalamus, VL=ventral lateral nucleus of the thalamus] *(Image by courtesy of C. Mantei)*

turn send, via the motor nuclei of the thalamus (VA/VL), information back to the motor cortex *(Trepel, 2003)* (see Figure 2.4-1, blue shaded area).

More specifically, information enters the striatum first, being subjected to complex integrative local processing. Finally, efferent fibers of the pallidum either enhance or suppress motor impulses in the thalamus, therefore also affecting the motor cortex. One of the most important functions of the basal-ganglia loop is the fine-tuning of a movement plan, particularly regarding the control of movement parameters like magnitude, direction, force and velocity. In addition to that, basal ganglia have been shown to be involved in the inhibition of inappropriate movement plans. Lesions to the basal ganglia have demonstrated to result most often in movement abnormalities as poverty of movement (e.g. akinesia) or involuntary movements (e.g. tremor).

2.4.2 Cortex - Pons - Cerebellum - Thalamus - Motor Cortex

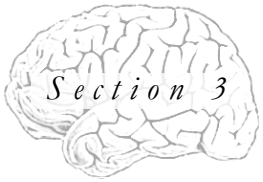
The second fine-tuning system is formed by associative cortical fibers reaching the pons and then being relayed to the contralateral cerebellum, which feeds back to the motor thalamus and then to the cortex (see Figure 2.4-1, red shaded area). This pathway is the most important route by which the cerebellar cortex can influence the cerebral cortex. The cortico-pontine projection carries information that the contralateral cerebellum uses to participate in the preparation to move and in the initiation and execution of movements. Amongst others, the cerebellum receives proprioceptive information, and integrates them in order to provide M1 with a smooth movement plan. Furthermore, the cerebellum has been intimately associated with coordination and timing functions.

2.5 Summary

The previous chapter has reviewed anatomical properties of the motor system that underlie most efficient motor control functions. Current concepts regarding the subdivision of motor regions were presented. There is much evidence for the existence of many dissociable non-primary motor regions on the lateral and medial surfaces of the brain, however, clear functional evidence that would justify such a highly specialized parcellation of motor areas in the human brain has yet to be supplied.

The primary motor cortex has shown to receive strong afferences from manifold cortical and subcortical regions. This provides support that its function spectrum goes beyond the pure transmission of motor output commands to the spinal cord. Its particular anatomical organization, such as the horizontal fibers spanning the entire M1 region, provides ideal preconditions for a direct involvement in motor learning.

The issue of M1 somatotopy which is situated at the border between structure and function has been intensely discussed here. In summary, existing studies support a gross somatotopy of major body parts; but there is no evidence for a strictly segregated fine-scale, within-limb organization. This leads to the question of a potential benefit of an intermingled, strongly overlapping functional arrangement – a question that has to be experimentally explored in future research.



FUNCTIONAL PROPERTIES OF THE MOTOR SYSTEM

Based on the underlying anatomical structure, which has been reviewed in the previous section, section 3 addresses the question of how parts of the human sensorimotor system interact to accomplish (skilled) motor action. Given the enormous manifoldness of the topic, this section primarily discusses functional properties of the primary motor cortex (M1) and its role in motor learning and consolidation. Special emphasis will be placed on the distinction between functional activation patterns associated with simple versus complex movements. Complex movements have been linked to a much more complex activation pattern, and hence training-related changes are rather intricate in nature, evident in many motor and non-motor areas. Since most existing training studies have been focusing on complex sequential movements, experiments of the present thesis were designed to assess neural changes accompanying the practice of most elementary finger tapping movements. Thereby the neural network of areas influencing the pattern of functional reorganization in M1 was intentionally held small.

3.1 Neural Control of Movements

The human brain seems to be very efficient in controlling skilled movements. We perform complex movements with no difficulty. Often we are not even aware of the enormous extent of control demands that skilled motor action is placing onto our motor cortices. Also, the human motor system yields a tremendous capability to learn new skills and retains this ability across life span. One of the most impressive abilities humans can achieve is the professional handling of a musical instrument. A pianist, for example, has to bimanually coordinate the production of up to 1800 notes per minute *(Munte et al., 2002)*.

3.1.1 Specification of the functional motor system

Movements are controlled by a hierarchically organized system consisting of cortical, subcortical and cerebellar structures. As a consequence of the complex interplay of these structures, information is relayed to motor neurons sitting in the spinal cord; their axons eventually project to muscle fibers. In other words, movements are produced by spatial and temporal patterns of muscular contractions coordinated by the brain and spinal cord.

As already mentioned in ▸Section 2.1.3 and 2.1.4, the following neural structures have been suggested to contribute to the control of movements:

- [1]Primary motor cortex (M1)
- [2]Lateral premotor cortex (PMC; dorsal PMd, ventral PMv)
- [3]Mesial premotor cortex (SMAproper, preSMA)
- [4]Cingulate motor area (CMA)
- [5]Frontal Eye Field (FEF)
- [6]Basal ganglia (BG)
- [7]Cerebellum (CB)

The motor areas of the lateral and medial frontal lobe [1-5], which are strongly interconnected, act in concert to mediate the planning and initiation of complex temporal sequences of voluntary movements. These cortical regions receive regulatory input from the subcortical structures [6, 7] via relays in the ventrolateral thalamus. Further modulatory input comes from the somatic sensory regions of the parietal lobe.

The involvement of these structures and the extent of their activation have been shown to strongly depend on task characteristics and effortfulness. Although there is no simple and clear definition of 'effortfulness', certain factors can be identified that do influence the amount of effort that is necessary to perform a certain movement. One such factor is the degree of complexity of a movement

that can be understood in a variety of ways (see below). Second, greater effort is required to produce movements with higher speed/rate or greater force. Hand dominance does also influence the degree of required effort; movements of the non-dominant hand necessitate more effort than movements of the dominant hand.

3.1.2 Neural control of simple vs. complex movements

One approach to define the complexity of a movement was introduced by Harrington et al. *(2000)*. According to their idea, the complexity of a movement is defined by its (1) *surface structure* and by its (2) *abstract structure (Harrington et al., 2000)*. The *surface structure* of a movement refers to properties such as the number of different effector muscles and joints involved or the number of movements that belong to a given sequence. The *abstract structure* of a sequential movement is exemplified by the relations between movement parts, such as repetitions or complex alterations (e.g., number of transitions in a sequence).

Behavioral investigations of sequential movements have revealed that increases in complexity prolong the time that is needed to plan a series of movements (referred to as reaction times). It has been suggested that this presumably reflects the greater amount of programming and encoding needed for each response in the sequence *(Rosenbaum et al., 1983)*.

Studies addressing the difference in the neural control of simple vs. complex movements have operationalized *complexity* in quite different ways. The impact of complexity on functional brain activity has been tested by comparing sequences of different lengths *(Sadato et al., 1996a; Wexler et al., 1997; Boecker et al., 1998; Gordon et al., 1998; Catalan et al., 1998; Haslinger et al., 2002)*, sequences of different types such as scale-like (consecutive, 5-4-3-2) vs. non-scale like (non-consecutive, 3-5-4-2) movement sequences *(Gerloff et al., 1997; Chen et al., 1997b; Gerloff et al., 1998; Haslinger et al., 2002)* or individual versus sequential finger movements *(Colebatch et al., 1991; Rao et al., 1993; Shibasaki et al., 1993; Wexler et al., 1997; Gerloff et al., 1997; Gordon et al., 1998; Jäncke et al., 2000a)*.

The apparent lack of definition of what exactly constitutes movement complexity is a likely cause of the heterogeneity of resulting findings. Complex movements in one study may be linked to neural activation patterns different from those associated with complex movements in another study. In general, increasing movement complexity has been associated with stronger neural activation within the sensorimotor network, with respect to both intensity and extent. Specifically, complexity-related increases in neural activation have been reported for the SMA *(Rao et al., 1993; Shibasaki et al., 1993; Gerloff et al., 1997; Gordon et al., 1998)*, for the lateral premotor cortex *(Colebatch et al., 1991; Rao et al., 1993; Sadato et al., 1996a; Boecker et al., 1998; Catalan et al., 1998)*, contralateral M1 *(Colebatch et al., 1991; Gordon et al., 1998; Gerloff et al., 1998)*, ipsilateral M1 *(Shibasaki et al., 1993; Sadato et al., 1996a; Wexler et al., 1997; Chen et al., 1997b; Gordon et al., 1998)* and thalamus *(Sadato et al., 1996a)*. Furthermore, activity in prefrontal and parietal regions has been repeatedly shown to be associated with complexity *(Rao et al., 1993; Sadato et al., 1996a; Gordon et al., 1998; Catalan et al., 1998)*.

Harrington et al. *(2000)* aimed to dissociate functional subsystems associated with the two classes of parameters defining complexity (surface and abstract structure; see above); and thus contributed to disentangle the complexity and heterogeneity of previous findings. According to their results there are some neural structures that are involved in the control of sequential movements regardless of their structural properties, but there are also regions that do specifically represent either the surface or the abstract properties. The authors provide evidence that surface properties (as operationalized by the number of involved fingers) correlate with activity in the cerebellum and superior parietal cortex while abstract properties (as operationalized by the number of required transitions) are mainly correlated with activation in inferior parietal and dorsal premotor regions. Ventral premotor and rostral inferior-parietal cortex activation were related to both properties of movement sequences.

It is obvious that a complex movement sequence places higher demands on cortical control mechanisms as for example simple repetitive finger tapping. Depending on the degree of complexity and difficulty (specified by the spatial-

temporal structure of the contractions of different muscles) of movement sequences, regions that are not classically considered as belonging to the sensorimotor system are recruited. Among those cognition-related regions are the prefrontal cortex (working memory, attention) and the parietal cortex (spatial transformations and encoding).

3.1.3 The rate effect: A question of effort

Several studies so far have tried to relate certain movement parameters to patterns of brain activation. The discharge rate of M1 neurons was found to correlate with a variety of kinematic and dynamic motor parameters, including force, direction, position and velocity *(Kalaska & Crammond, 1992)*. As mentioned above, greater effort (and therefore greater neural activity) is required to produce movements of greater force or speed. Given that movement rate is a central issue of this thesis (the investigated motor training aimed to increase maximum thumb tapping speed), this section will particularly focus on previous literature assessing the pattern of neural activity at different movement rates. There is strong evidence that the primary motor cortex is heavily involved in controlling subjects' maximum tapping speed. Single-cell recording studies in monkeys have demonstrated that the discharge activity of M1 motor neurons correlates robustly with the velocity of the movement *(Humphrey, 1972; Ashe & Georgopoulos, 1994)*. More recent support comes from several neuroimaging studies that have consistently proven a *rate effect* for M1 *(Schlaug et al., 1996; Sadato et al., 1996b; Jäncke et al., 1998a; Jäncke et al., 1998b; Lutz et al., 2005)*. In addition, Toma et al. *(2002)* showed that task-related alpha-power changes, as measured with electroencephalography (EEG), are also sensitive to reveal a neural rate effect. Another very recent study by Jäncke et al. *(2004)* demonstrated a decrease in maximum finger tapping speed when the function of M1 was disrupted by low-frequency rTMS. Although there is a consensus that increasing movement velocity is generally associated with increased activation in cortical motor areas, the issue of linearity of this relationship has not been sufficiently explored. It appears from existing work that a linear relationship between rate and activation does not hold for all brain regions and for all frequencies *(Jäncke et al., 1998a; Jäncke et al., 1998b)*. It has been proposed that the *rate effect* is due to increasing

processing demands placed on the motor areas with increasing movement rates. In addition, finger tapping at maximum speed is thought to require the contralateral primary motor area to operate at a maximum activation level. A very recent study has provided evidence that the amount of neuronal effort (reflecting the control demand that is necessary to control the tapping movement) is the critical variable determining the activation within M1 and not the physical tapping speed *(Lutz et al., 2005)*. It was shown that maximum-speed tapping using either the left or right index finger caused similar amounts of contralateral M1 activity, although the maximum tapping rate was different for the two hands.

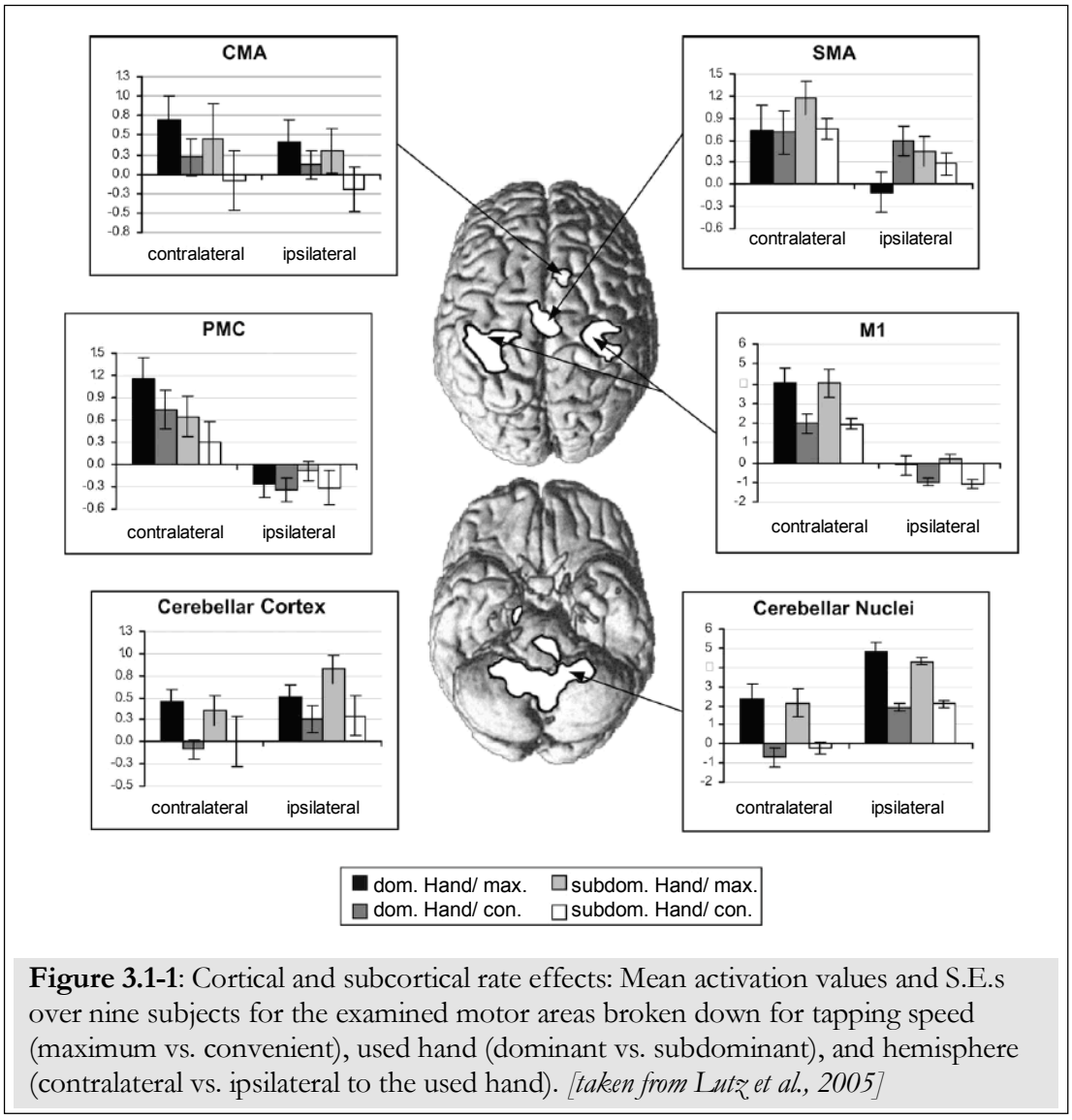


Figure 3.1-1: Cortical and subcortical rate effects: Mean activation values and S.E.s over nine subjects for the examined motor areas broken down for tapping speed (maximum vs. convenient), used hand (dominant vs. subdominant), and hemisphere (contralateral vs. ipsilateral to the used hand). *[taken from Lutz et al., 2005]*

Besides M1, several non-primary motor areas like the cerebellum, and partly medial and lateral premotor cortices adjust their activation to the increase of ef-

fort accompanying a higher rate of movement *(Schlaug et al., 1996; Sadato et al., 1996a; Jenkins et al., 1997; Jäncke et al., 1998a; Jäncke et al., 1998b; Lutz et al., 2005)*. As for the cerebellum, the observation of rate-related activity is not surprising given the strong connections that it maintains with M1. However, the issue of rate effects in premotor regions needs future exploration. Corresponding findings are inconsistent and appear to be confounded with movement complexity.

3.1.4 Neural correlates of hand dominance (hemispheric asymmetry)

Previous studies have provided evidence that the degree of involvement of the ipsilateral hemisphere in the control of unimanual movements is influenced by *hand dominance*; while the dominant left hemisphere is involved in both, left and right hand movements, the subdominant right hemisphere is mainly active with left hand movements *(Kim et al., 1993; Chen et al., 1997b; Baraldi et al., 1999; Cramer et al., 1999; Caramia et al., 2000; Alkadhi et al., 2002b; Kobayashi et al., 2003; Huang et al., 2004; Verstynen et al., 2005)*. This has been linked to the fact that the subdominant motor cortex might operate at suboptimal control levels *(Jäncke et al., 1998b; Lutz et al., 2005)*. Movements of the subdominant hand, that are generally much less skilled compared to dominant-hand movements, are associated with higher processing demands. Thus, the discrepancy between pronounced needs of neural control and the insufficient capabilities of the contralateral cortex is likely to explain the additional involvement of the ipsilateral M1 in case of subdominant hand movements. A recent study by Agnew et al. *(2004)* provides one putative explanation for the observation that the right hemisphere system is less skilled at controlling variable rate finger movements. The main finding of this study is that rate-related activity was limited to the left hemispheric corticostriatal loop (precentral gyrus, thalamus, and posterior putamen) during movements with the dominant right hand. The authors explain the lack of rate-related activity in the right hemisphere during left-hand movements as follows: The right hemisphere motor system becomes maximally engaged already at a low movement rate and is therefore not further modulated when movement speed is increased. In conclusion, this finding suggests that "the specialization

of the left hemisphere corticostriatal system for dexterity is reflected in asymmetric mechanism for movement rate control" (p. 289).

3.1.5 Specific aspects of M1 function

The idea of M1 functionality has considerably changed during the past 20 years of pertinent research. First of all, the proof of the impressive capability of the entire neural system for structural and functional reorganization (as outlined in ▸Section 1) has strongly influenced the understanding of the functional properties of the primary motor cortex. Second, there is evidence that the classical view of M1 as a strictly somatotopically organized area only applies for major body divisions; however fine-scale somatotopy has been contested. Third, beyond the primary role M1 plays in the control of muscle action patterns, it appears to be strongly involved in motor learning and consolidation of motor skills. Fourth, M1 seems to be involved in higher aspects of motor cognition, such as motor imagery. The focus of this section is placed on the complex functional architecture of M1 which is a prerequisite for reorganization and skill learning. The issue of somatotopy has already been addressed in ▸Section 2.2.2. The role of M1 in motor skill learning and corresponding examples of M1 plasticity will be discussed in ▸Section 3.2.3.

The understanding of M1 functioning is based on the understanding of underlying organization principles of the corticospinal motor system. Functional divergence and convergence have been shown to be basic principles of corticospinal architecture *(for a detailed review see Hepp-Reymond, 1988)*. First, many M1 neurons have direct projections to the spinal motor neuron pools of multiple muscles *(Shinoda et al., 1979; Nudo et al., 1992)*. Second, the enormous convergence onto the spinal motor neuron pool of a given hand muscle from large M1 territories was outlined *(Phillips & Porter, 1977)*. Consistent with these two findings, certain M1 neurons appear to be active with multiple hand motor actions *(Schieber & Hibbard, 1993)*. Third, a substantial system of horizontal connections indicates that upper motor neurons do not exclusively send output to the spinal cord but, in addition, participate in internal cortical information processing. Taken together, these organization principles indicate that single M1 output neurons act

to facilitate synergistic combination of muscles. On the other hand, it has been proposed that the motor cortex functions to individuate movements, "to sculpt movements of a particular body part out of a group movement", by means of suppressing some muscles via inhibitory circuits. This idea was supported by data showing that lesions in M1 principally impair individuated movements of distal body parts *(Schieber & Poliakov, 1998)*. In conclusion, it was suggested that complex or continuous movements are initiated by some output neurons, while other neurons function to individuate a more simple or discrete movement.

The horizontal fiber system that spans the entire M1 area (especially evident in layers II, III and V) is thought to be the neural substrate enabling the tremendous amount of functional plasticity. By unmasking of horizontal connections the system can promote the establishment of dynamic motor maps constructed by distributed neural assemblies *(for details see Sanes & Donoghue, 2000)*. This seems to be the basic mechanism M1 likely uses to flexibly adapt to changed environmental pressures and conditions (e.g. learning of a new skill or functional recovery after cortical lesions). Moreover, horizontal fibers were shown to have the capacity for long-lasting synaptic modification (LTP / LTD; see above in ▸Section 1.2.1). Those persistent synaptic modifications are considered to constitute the basis for longer-lasting efficiency of horizontal connections.

3.2 Motor Learning & Functional Plasticity

Motor skill acquisition refers to the process by which movements come to be performed effortlessly through repeated practice. In the context of basic research, studies have tried to identify neural substrates that mediate motor skill learning by using two gross experimental strategies. *Motor sequence learning* refers to the incremental acquisition of sequential movements into a well-executed behavior whereas *motor adaptation learning* rather tests our capacity to compensate for environmental changes *(for a review see Ungerleider et al., 2002)*. When reviewing previous studies on motor learning and functional plasticity in the sensorimotor system it appears that most studies used more or less complex motor behavior (motor sequences or synergies). Learning of such complex motor tasks is generally accompanied by activation changes in the contralateral motor cortex but

also in secondary motor areas and modifications in cortico-striatal and cortico-cerebellar loops that are serving task performance *(for a review see Doyon & Benali, 2005)*. Neural changes associated with modifications of single parameters of a simple movement have been insufficiently explored and incompletely understood. In the following, a short overview on neural changes accompanying the acquisition of complex skills will be given, but the main focus will be placed on changes linked with the performance and practice of elementary movements.

3.2.1 Complex motor skill learning

The majority of studies that have addressed functional plasticity in the motor system can be counted among either *motor sequence* or *motor adaptation learning* - mostly limited to the upper extremity. Training durations did usually not exceed 30 minutes (which corresponds to one training session). Often used experimental paradigms include (a) learning of finger movement sequences of different complexity, (b) serial reaction time tasks to differentiate between implicit and explicit learning and (c) the adaptation of a movement to compensate for environmental changes or disturbances. While an extensive amount of work has been carried out to explore the effects of short lasting trainings *(Grafton et al., 1992a; Hazeltine et al., 1997; Shadmehr & Holcomb, 1997; Jueptner et al., 1997a; Jueptner et al., 1997b; Toni et al., 1998; Grafton et al., 2002; Morgen et al., 2004; Garry et al., 2004; Floyer-Lea & Matthews, 2004)*, longer training intervals have for several obvious reasons received little attention so far *(Pascual-Leone et al., 1994; Karni et al., 1995; Hlustik et al., 2004; Nyberg et al., 2006)*.

Doyon & Benali *(2005)* have recently introduced a model that describes changes in cortico-striatal and cortico-cerebellar circuits that accompany motor skill learning. They expand earlier models (e.g., the two-stage-model of Ungerleider, 2002) and propose 5 stages in the process of motor learning:

i. a fast early learning stage in which considerable improvement in performance can be observed across the initial training session

ii. a slow learning phase with further gain in performance across several training sessions

iii. a consolidation stage in which performance can spontaneously improve without further practice about 6 hours after the initial training session,

iv. an automatic stage during which a skilled behavior is considered to require minimal cognitive resources

v. a retention stage in which motor skill can be readily executed after long periods in which the movement has not been performed

Basically, the model proposes that in the early stages of both types of skill learning the entire motor network (primary and secondary motor cortices, cerebellum, basal ganglia, and parietal cortex) is involved. Dynamic interactions between parts of this network are considered to be crucial in order to set up motor routines that form the basis of skill learning. After consolidation has occurred and after the performance has become automatic, more specific subnetworks serve to control a motor skill dependant on the particular nature of the skill. The model assumes that during *motor adaptation* the basal ganglia (specifically the striatum) are not longer necessary for retention and performance while the cortex in collaboration with the cerebellum is capable to ensure proper task performance. In case of *motor sequence learning* parts of the cerebellum are not longer needed, but instead the basal ganglia keep functional connectivity with the cortex to accomplish motor performance.

This model does not make specific predictions on how intracortical circuits might change in response to training. Generally it has been suggested that activation is shifted posterior with training and with reduced cognitive demands required by a particular motor skill. With proceeding skill learning, activity has been shown to move from the anterior preSMA towards the more posterior SMA proper. Furthermore, activity in prefrontal (attention and working-memory related) regions decreases *(Grafton et al., 1992a; Shadmehr & Holcomb, 1997; Jueptner et al., 1997b; Grafton et al., 2002)*. The role of the primary motor cortex in motor skill learning and related findings will be discussed in ▸ Section 3.2.3.

3.2.2 Repetition of elementary movements

Compared to complex skill learning, considerably less data are available on motor learning of more elementary movements, such as finger flexion/extension. Those movements are frequently performed in daily life and form the basis of more complex, purposeful motor acts. Several studies have been conducted in order to examine changes in neural activation accompanying the stereotyped repetition of elementary movements *(Yetkin et al., 1996; Rajah et al., 1998; Dejardin et al., 1998; Carey et al., 2000b; Loubinoux et al., 2001; Tracy et al., 2001; Morgen et al., 2004)*. In the majority of earlier studies simple finger movements have been considered suitable to test reliability of data acquisition techniques as fMRI or PET - an idea that is not compatible with current concepts of plasticity. Later studies have taken the issue of plasticity into account and looked for changes in neural activity while ensuring constant behavioral output during the measurements to avoid direct contribution of altered behavior on brain activity and thus to minimize confounds *(Freude & Ullsperger, 1987; Dirnberger et al., 2004; Halder et al., 2005)*. Up to now only very few studies have explicitly investigated changes in neural activity that are directly linked to the modification of a single movement parameter (such as direction, acceleration or speed).

One experimental paradigm that is widely used was introduced by Classen and co-workers *(1998)*. Using TMS, they have elegantly shown that the stereotyped repetition of a simple finger movement for a period of 30 minutes results in distinct plasticity effects within M1. Their results strongly suggest the establishment of a memory trace that served to encode kinematic details of the practiced movement *(Classen et al., 1998; Classen et al., 1999)*. Specifically, the preferred direction of TMS-induced thumb movements was assessed and this information was used to adapt the subsequent motor training. The rational was to practice thumb movements in the direction contrary to the preferred direction as determined at initial TMS measurements. Interestingly, the training resulted in a change of the preferred TMS-induced direction of thumb movements towards the trained movement direction. The authors have interpreted this effect as reflecting a short-term memory for movement. Subsequent studies that aimed to elucidate the underlying neurophysiologic mechanisms serving the observed ef-

fect have shown an influence of NMDA, muscarinic and alpha-adrenergic receptor function but also GABAergic neurotransmission *(Butefisch et al., 2000; Sawaki et al., 2002a; Sawaki et al., 2002b)*. A recent fMRI study by Morgen et al. *(2004)* exploited the same experimental paradigm and revealed task-specific reductions in M1/S1 when comparing post- to pretraining measurements.

In summary, there are some studies that have assessed the question of neural adaptation to the repetition of elementary movements, but the resulting findings are controversial, likely due to differences in the used motor tasks and techniques. While some studies show consistency of the neural activity *(Yetkin et al., 1996; Carey et al., 2000b; Loubinoux et al., 2001)*, others demonstrated increases or decreases during the course of one experimental session *(Freude & Ullsperger, 1987; Rajah et al., 1998; Dejardin et al., 1998; Tracy et al., 2001; Dirnberger et al., 2004; Halder et al., 2005)*. As mentioned above, within-session reductions have been reported related to practice of simple movements aimed to modify a particular parameter *(Morgen et al., 2004)*. Using fMRI but focusing on the acquisition of a complex motor sequence, Karni et al. *(1995)* did also report adaptation-like reductions in activity at the end of the first training session. These results suggest that the motor system optimizes its efficiency of motor control even during repetition of a simple overlearned movement and when effort is kept constant across practice trials. One possible mechanism underlying enhanced efficiency on a cellular level relates to LTP-like mechanisms. It has been speculated that existing movement representations need to be partially broken up in order to set up new or refined movement representations. This may be mediated by a down-regulation of the lateral GABAergic inhibition that would lead to a transient increase in neural excitation. As a consequence, the removal of the Mg^{2+} from the NMDA receptors would be enhanced and this would finally cause the facilitation of NMDA-mediated long-term potentiation mechanisms *(Butefisch, 2004; Halder et al., 2005)*.

3.2.3 The role of the primary motor cortex in motor learning

The primary motor cortex has been traditionally associated with motor output commands that it sends to the muscles via the corticospinal tract. Current con-

cepts of M1 function, however, go beyond this pure output function and acknowledge that it belongs to the network of brain regions serving the acquisition of motor skills *(Karni et al., 1995; Honda et al., 1998; Muellbacher et al., 2002)*. First, M1 has been proven to make important contributions to the learning of new skills after the actual practice session and has thus been suggested to play a critical role in consolidation, a process that contributes to make a skill less susceptible to interference *(Brashers-Krug et al., 1996; Shadmehr & Holcomb, 1997; Muellbacher et al., 2002; for a review see Krakauer & Shadmehr, 2006)*. Only recently, another process that has been referred to as "off-line learning" *(Robertson et al., 2005; Press et al., 2005)* has been shown to take place in M1 between training sessions and is rather linked to skill improvement. Interestingly, M1 appears not to be involved in over-night off-line learning but is exclusively important for off-line learning during the day *(Maquet et al., 2003; Robertson et al., 2005)*.

There is a wealth of evidence for training-induced changes in M1 activation, both from short- and long-term motor practice studies. These findings corroborate the critical role M1 is playing in the processing and storage (consolidation) of new motor information. Regarding the initial fast learning stage that is linked with a pronounced within-session improvement of performance, data from existing studies do not provide a clear neurophysiologic substrate. While some

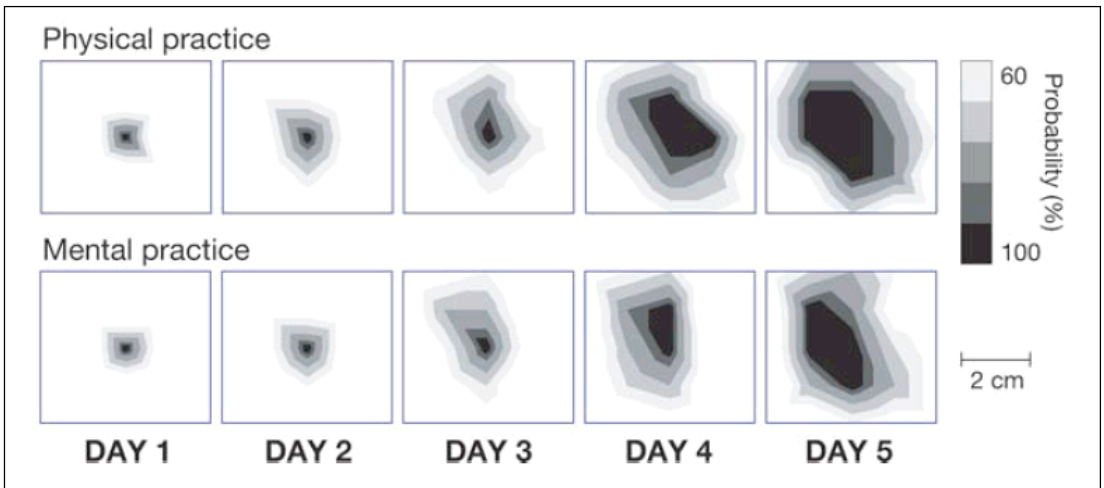


Figure 3.2-1: Changes in cortical output maps associated with learning a five-finger exercise on the piano (modified from Pascual-Leone et al. 1995, 1996): Average cortical output maps for the finger flexors of the trained hand in subjects undergoing daily physical versus mental practice. *(Figure taken from Pascual-Leone et al. 2005)*

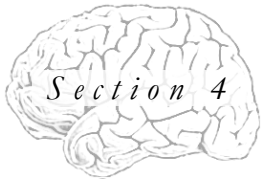
studies report increases of M1 activity during the course of the first training session *(Hazeltine et al., 1997; Grafton et al., 1998)* others have provided evidence for activation decreases *(Jenkins et al., 1994; Karni et al., 1995; Toni et al., 1998; Doyon et al., 2002; Morgen et al., 2004; Floyer-Lea & Matthews, 2004)*. TMS-based work, that assesses excitability of the corticospinal system in the absence of movement, indicates increased M1 activation after the accomplishment of a short motor training *(Muellbacher et al., 2001; Garry et al., 2004)*.

In contrast, the slow learning stage has consistently been associated with marked increases in M1 activation during performance of the trained movement *(Karni et al., 1995; for a review see Ungerleider et al., 2002; Hlustik et al., 2004; Floyer-Lea & Matthews, 2005; Nyberg et al., 2006)*. As displayed in Figure 3.2-1, enlargements of functional M1 muscle representations as a result of physical or even mental training were also demonstrated using TMS *(Pascual-Leone et al., 1994; Pascual-Leone et al., 1995)*.

As already mentioned in ▸Section 1.4.1, intensive lifelong training, as it is the case for professional musicians and sportsmen, leads to a more efficient mode of motor control; skilled compared to unskilled subjects show decreased activation when performing a given motor task. This effect has been commonly associated with diminished neural effort necessary to perform the movements *(Krings et al., 2000; Jäncke et al., 2000c; for a review see Munte et al., 2002)*. In summary, the described activation patterns are consistent with the idea that more neuronal involvement is needed at the beginning of training in order to build up a larger network or to implement task-specific routines. This increase in processing capacities may be the basis for shaping more efficient networks at later training stages.

3.3 Summary

Motor Skill learning has been intensely investigated during the last two decades. However, the majority of cases used rather complex movements that were learned within shortly lasting trainings (mostly not exceeding a single training session). The acquisition of complex motor skills has consistently been associated with changes in cortical activation patterns but also with changes in cortico-striatal and cortico-cerebellar motor loops. Corresponding findings have also lead to modifications in the understanding of the functional role of M1. There is strong evidence that M1 is extensively involved in motor learning and consolidation processes. Particularly the system of horizontal connections which spans M1 has been proven to be one substantial neural substrate of functional reorganization. Compared to the large amount of work that has been carried out on complex movements, motor practice of elementary movements with the accompanying modification of basic movement parameters such as speed, acceleration or force has received comparatively little attention. Additional studies are needed to reveal underlying substrates and principles. Furthermore, medium training durations in the range of weeks have been rarely used in the past. Most studies up to now have either concentrated on short-term training effects or assessed changes in functional motor control resulting from life-long training, thus leaving many interesting questions to be addressed in the future.



Section 4

METHODS FOR STUDYING TRAINING-RELATED CHANGES

Neuroimaging techniques provide powerful methods for studying anatomy and function of the human brain. Publication 1 uses Transcranial Magnetic Stimulation (TMS) to assess training-related changes in corticospinal excitability. Publication 2 makes use of the most obvious advantage of current functional magnetic resonance imaging (fMRI) techniques, namely its high spatial resolution, to delineate and characterize finger-specific brain activation patterns. Finally, Experiment 3 was conducted using conventional Electroencephalography (EEG) combined with LORETA to identify and localize changes in oscillatory activity accompanying motor training. This section describes the underlying physical and physiological principles of fMRI, TMS and EEG and addresses methodological issues specific to the scope of the publications.

4.1 Transcranial Magnetic Stimulation (TMS)

Transcranial Magnetic Stimulation (TMS) has become extremely popular to non-invasively study human brain function. In contrast to other techniques, TMS can demonstrate causality. Neuroimaging methods, such as fMRI or PET, allow the identification of brain regions that are activated when a subject performs a particular task. However, this does not verify that those regions are actually used to accomplish the task. TMS allows suppressing activity in a certain region and alters the resulting behavior. If the subjects' task performance is impaired, this supports the notion that the region

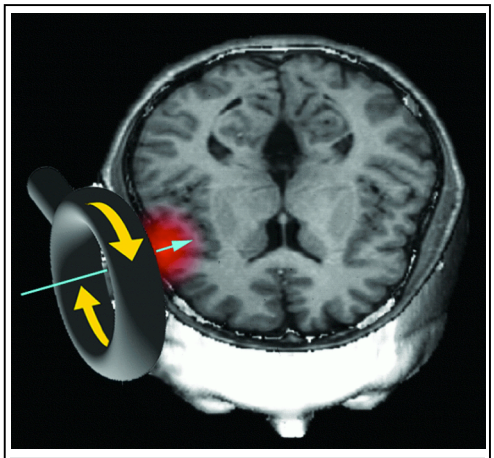


Figure 4.1-1: The basic principle of TMS. *(Image by courtesy of A. Pascual-Leone)*

is needed for performing the task. The first TMS device was built by Anthony Barker *(Sheffield / England) (Barker et al., 1985)*. Since this first practical application the TMS technique has greatly advanced. While originally developed to assess the integrity of central motor pathways, it has now been established as a valuable tool to study localization of brain function and connectivity patterns between brain regions. Besides assessing cortical functions, TMS appears promising as a treatment for some neuropsychiatric diseases such as depression, Parkinson's disease, stroke, or obsessive-compulsive disorder.

4.1.1 Physical Principle of TMS

TMS is based on the principle of electromagnetic induction which refers to the production of an electrical potential difference across a conductor situated in a changing magnetic flux. Almost two centuries ago Faraday discovered that an electrical current flowing through a coil of wire generates a magnetic field that in turn can cause current to flow in a second coil. Applying this principle in TMS, the second coil is replaced by neural tissue. The fact that neurons generate weak electrical currents as a result of electrochemical events occurring in the context of neural signaling proves that electromagnetic induction can effectively influence neural functioning. This constitutes the basis for TMS.

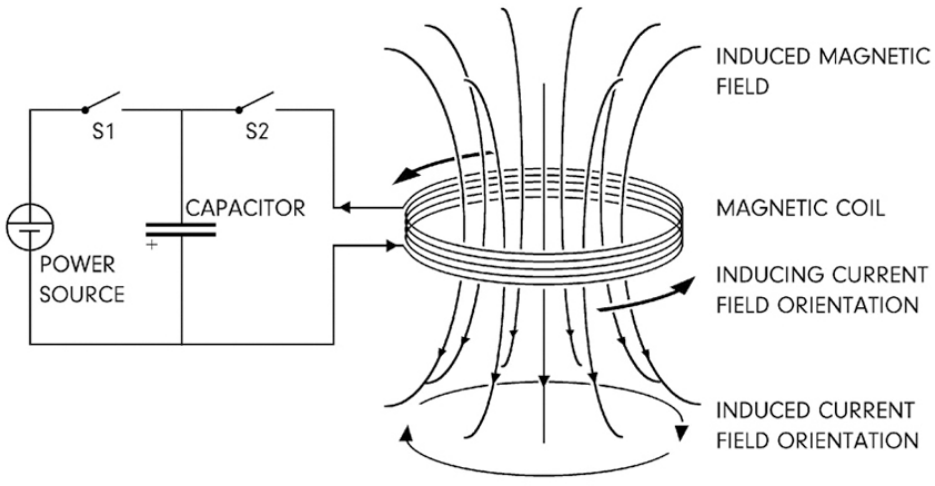


Figure 4.1-2: The technical principle of TMS. *(Figure taken from Rösler et al., 2001)*

In more detail, a magnetic stimulator works by charging one or more energy-storage capacitors and then quickly transferring the rapidly changing current

from the capacitor(s) to the coil of wire that is placed on the scalp. This current in turn produces a rapidly changing magnetic field that passes through the scalp into the underlying neural tissue, where it again induces an electrical field. Unlike electrical fields, magnetic fields are hardly attenuated as they pass through the skull. When sufficiently strong, the induced electrical current will stimulate neurons by penetrating their membranes, resulting in excitatory (or inhibitory) postsynaptic potentials or in an action potential (AP) *(Terao & Ugawa, 2002; Walsh & Pascual-Leone, 2003; Nollet et al., 2003)*.

Two physical principles define the effects of TMS. First, the induced current in the brain flows in a plane parallel to the surface of the coil, thus parallel to the cortical surface of the brain (see figure 4.1-2). It has been suggested that TMS does particularly affect neurons with axons or dendrites oriented parallel to the brain surface, since in that case an electrode voltage can be built-up between different locations of the dendrite or axon. Second, the induced magnetic field falls off rapidly with distance from the coil, thus making a direct effect onto structures deep in the brain very unlikely. Currently used stimulators and coils can produce maximum magnetic fields of 1.5 to 2.0 T along the winding of the coil, and are capable of activating neurons that lie 1.5 to 2.0 cm below the scalp surface. However, the use of specially designed coils and sufficiently high stimulation intensities enables the activation of cortical areas lying at a depth of about 3 to 4 cm (e.g. the leg motor area). The strength of the induced electric field mainly depends on the rate of change of the magnetic field, which, in turn, depends on the rate of change of the electrical current in the coil.

4.1.2 Physiological basis of TMS

There has been a considerable debate as to which neural structures or elements are specifically affected by the application of a TMS pulse ever since the TMS method was first introduced.

When applied to the motor cortex, TMS pulses evoke multiple descending volleys in corticospinal neurons. The initial volley has been suggested to arise from

direct excitation of pyramidal cells at the region of their axon hillock (D-wave: direct wave). The D-wave is followed by several indirect waves (I-waves) at intervals of about 1.5ms. There still is much uncertainly about the origin and particularly about the periodicity of I-waves, however it is thought that they are produced by transsynaptic excitation of the same corticospinal neurons. Transcranial Electrical Stimulation (TES) was shown to directly activate corticospinal fibers, thus leading to D-waves that migrate down the pyramidal system. In contrast, comparatively weak magnetic stimuli such as near-threshold forms of TMS activate corticospinal neurons indirectly and therefore only evoke a series of I-waves *(Day et al., 1989; Di Lazzaro et al., 1998a; Di Lazzaro et al., 1998b)*. Temporal and spatial summation of the descending volleys reaching spinal motor neurons is necessary to cause their discharge. In case of motor cortex stimulation the physiological effect of TMS can easily be quantified by measuring the size of motor evoked potentials (MEP) induced in contralateral muscles. Depending on the current excitability of motor neuron pools and on the stimulation strength, some spinal cord neurons will reach their firing threshold and some will not, thus contributing to the enormous variability of MEP size and shape in response to consecutive TMS pulses.

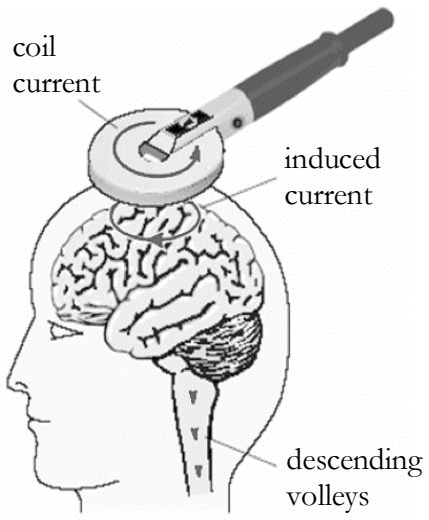


Figure 4.1-3: Basic principle of evoking MEPs by means of TMS. *(Figure modified from www.magstim.com)*

4.1.3 Stimulation characteristics and parameters

In a recent review, Sack & Linden *(2003)* have dissociated between *stimulation parameters*, which describe physical properties, and *stimulation characteristics* referring to the physiologic effect of the stimulation.

4.1.3.1 Stimulation parameters

Physical parameters of TMS include intensity, amplitude and frequency of the pulse, pulse duration and rise time, as well as the characteristics of the induced magnetic field.

4.1.3.2 Stimulation characteristics

The strength and distribution of the induced electric field are the most important variables to determine physiologic effects since they influence the depth of penetration and the spatial accuracy of the stimulus. Stimulation characteristics are in turn influenced by many factors including coil geometry and size, anatomical properties of the subject, physiological properties of the tissue to be stimulated, and of course by the above mentioned stimulation parameters.

Coil geometry. Shape and size of the coil are the main factors to determine the size of the stimulated area. Typically, two types of coils are used in neuroscientific research: circular and so-called figure-of-eight coils. The electric field produced by a circular coil is diffuse. The induced current flows in a region underneath a circular that is usually approximately between 8 and 12 cm in diameter. Generally, larger circular coils can stimulate more effectively deeper cortical structures compared to smaller coils. In case of figure-of-eight coils, the induced field is more concentrated and stronger compared to circular coils. The maximum of induced current is directly under the intersection of the two wings *(Rothwell, 1997; Hallett & Chokroverty, 2005)*, thus enabling to stimulate with a better spatial accuracy.

4.1.4 Different TMS techniques

There are several possibilities to employ the TMS technique for assessing cortical functions *(Kobayashi & Pascual-Leone, 2003)*. Since TMS is mostly painless and has no adverse side effects, it has been established as a routine method in clinical neurophysiology. While initially it was mainly used for assessing corticospinal conduction, it is in the meanwhile investigated as a tool to treat psychiat-

ric disorders such as depression or obsessive-compulsive disorder *(Fregni & Pascual-Leone, 2005a; Fregni & Pascual-Leone, 2005b)*. The spectrum of application however goes well beyond the clinical setting. Nowadays, TMS is used to assess a variety of cognitive and motor functions, and complements neuroimaging and electrophysiology in a very efficient way. Since experiment 1 (see Section 6) is based on single-pulse TMS, the main focus of the following section will be placed on this particular TMS application.

4.1.4.1 Single-pulse TMS

In healthy subjects, the size of motor evoked potentials (MEPs) is influenced by excitability changes of cortical and spinal motor neurons. Hence recording MEPs can be used to probe the excitability of the corticospinal tract under various experimental settings or compared to an individually defined baseline.

Since the size of the MEPs also strongly depends on the location of the coil on the scalp this method is well suited to produces so-called motor output maps, that serve to determine the cortical area that sends projections to a given muscle *(Pascual-Leone et al., 1994; Thickbroom et al., 1999; Triggs et al., 1999)*. Applying motor mapping techniques for a given muscle, a *hot spot* for that muscle can be obtained, meaning the scalp location from where TMS evokes the largest and most consistent MEPs for a given muscle. These *hot spots* follow the rough, large-scale pattern of somatotopy and are in good agreement with activation centers revealed in functional imaging. However it must be considered that the performance of movements when studied with fMRI, PET or MEG is accompanied by activation of M1 but also to a large degree of S1. Since sensory and motor activation are merged in most cases, the activation centers are shifted posteriorly when compared to the *hot spots* revealed by purely motor cortex based TMS *(Herwig et al., 2002; Lotze et al., 2003a)*. A very recent study, however proved a very convincing agreement of activation maxima across methods when comparing motor TMS of a given muscle with fMRI activ-

ity maps obtained while subjects performed motor imagery *(Nyazov et al., 2005)*.

MEPs are extremely variable in size and shape, much more variable than for instance peripherally evoked muscle potentials (CMAPs). This is mostly due to the complex nature of the physiologic corticospinal cascade evoked by a TMS pulse applied to the cortex. Specifically, the variability is attributed to the interplay of descending volleys in corticospinal axons and to differences in excitability of intervening synapses *(Kiers et al., 1993)*. To account for the high variability in MEP amplitude and to increase the reliability of the data, it is recommended to average across several stimulation trials.

The experimental study reported in ▸Section 6 of this thesis used single-pulse TMS to assess training-related changes in corticospinal excitability. A detailed description of the stimulation parameters used and information about the experimental protocol is given in ▸Section 6.3.

There are several possible causes for a change in corticospinal excitability measured with surface electromyography (EMG). Particularly in the context of motor training it is important to ask at what level the changes might have occurred (for instance: cortex, brain stem, spinal cord, peripheral nerves). There are several ways to address this question:

i. In order to control for changes of nerve and muscle excitability, maximal compound muscle action potentials (CMAPs) can be elicited by supramaximal electrical nerve stimulation *(Rossini et al., 1994; Ziemann et al., 1998b)*.

ii. Spinal roots can be stimulated by placing the magnetic coil over the cervical and lumbar spinal enlargements.

iii. Brain stem stimulation can be accomplished by placing a double-cone magnetic coil over the back of the head, thus stimulating descending motor pathways and recording an

MEP in arm or leg muscles. However, stimulation at brainstem or spinal levels is quite unpleasant for the subject.

iv. Assessing the Resting Motor Threshold (RMT) has been shown to provide information about the extent of neuronal membrane excitability. Different studies reported that the RMT is influenced by drugs that affect sodium and calcium channels, but not by those altering GABA or glutamate transmission *(Ziemann et al., 1996; Hallett, 2000)*. RMT is defined as the lowest TMS stimulator intensity capable to elicit a small MEP of usually 50 μV in response to 50% of the applied pulses.

In the TMS experiment reported in ▸Section 6 we determined the RMT, and we additionally recorded peripherally evoked CMAPs (maximum M-wave) to exclude the possibility of changes in nerve and muscle excitability. In that experiment, facilitation at the level of brain stem or spinal cord is unlikely. This issue is discussed in detail in ▸Section 6.5.

4.1.4.2 Paired-pulse TMS

Paired-Pulse experiments are designed to obtain information about the intracortical circuitry. There are a variety of techniques which allow the investigation of connections within M1 or connections between M1 and other cortical areas. Kujirai et al. *(1993)* were the first to show that a subthreshold conditioning stimulus suppresses a test stimulus that is applied between 1 to 6 msec after the first stimulus. This phenomenon – called short interval intracortical inhibition (SICI) – has been explained by the capacity of the conditioning stimulus to suppress the recruitment of descending volleys by the test stimulus *(Di Lazzaro et al., 1998c)*. In contrast if the two stimuli are separated by 10 to 15 ms, the response to the test stimulus is facilitated (long interval intracortical facilitation). Depending on where the two stimuli are applied, information is obtained on intraregional, interregional or interhemispheric connectivity. Many studies have used diverse paired-pulse TMS protocols in order to test pharmacologi-

cal effects of certain drugs *(see for instance, Ziemann et al., 1996; Ziemann et al., 1998a)*.

4.1.4.3 TMS as a virtual lesion technique

As mentioned above, TMS as virtual lesion technique is unique among methods used to study the human brain.

One usually differentiates between so called on- and offline TMS application designs *(for an overview see Robertson et al., 2003)*. In case of online TMS application, both stimulation and task performance occur concurrently. The approach of offline TMS refers to the application of TMS pulse trains before the behavioral task is going to be performed. While single- and double pulse but also repetitive TMS can be used with the online-TMS intervention, only repetitive TMS is suitable for the offline-TMS method.

Without going in too much detail, it has to be pointed out that the efficiency of single or double TMS pulses in online disrupting function strongly depends on the spatial and temporal precision. One evident problem is that the necessary information about the exact location and temporal characteristics of information processing is not sufficient in many functional sub-systems.

Regarding rTMS protocols, there is a differential effect of the stimulation frequency on the physiologic outcome. In case of online protocols, it was shown that high-frequency rTMS leads to an online-disruption of function; the higher the frequency of stimulation the greater the disruption of the target function *(Pascual-Leone et al., 1991)*. In contrast, high repetitive TMS (> 5 Hz) in the context of an offline TMS paradigm has been demonstrated to increase cortical excitability *(Berardelli et al., 1998; Maeda et al., 2000)*. However, up to now there are no convincing studies proving that high-frequency offline-rTMS has beneficial effects on cognitive or motor functions. In offline-rTMS paradigms 1-Hz stimulation is usually applied in order to efficiently induce virtual lesions.

First evidence that online applied TMS pulses disrupt cortical functions came from studies of the visual cortex *(Maccabee et al., 1991; Amassian et al., 1993)* and the motor cortex *(Day et al., 1989)*. More recent studies have used offline-rTMS at 1 Hz to investigate a variety of cognitive and motor functions *(e.g., Jäncke et al., 2004)*. Evidence for cross-modal plasticity in blind subjects has been provided by transiently inhibiting the visual cortex with rTMS which induced a temporary impairment of Braille reading abilities *(Sadato et al., 1996a; Merabet et al., 2005)*. The exact mechanisms by which rTMS disrupts cortical function is still under debate. It is suggested that the inhibitory effect of rTMS is due to the fact that it effectively introduces noise to a given cortical area by simultaneously stimulating large neuronal populations. This temporal reduction in signal to noise ratio will therefore interfere with structured task-relevant processing. The extent to which cortical processing is disturbed (hence whether or not a behavioral change can be observed) depends on the parameters of TMS stimulation (such as intensity, duration, frequency).

4.1.5 Spatial and temporal resolution of single-pulse TMS

One important issue defining the spatial resolution of TMS certainly relates to the magnetic coil that is used in a given experiment, as the coil properties influence stimulation characteristics (see above). However, an evident problem here is that the spatial characteristics (extent, distribution) can only be estimated by coil properties. It has been proposed that in case of figure-of-eight coils the activated cortical region is as large as the midregion of the coil which is about 3 – 4 cm^2 in commonly used coils *(Bailey et al., 2001; Siebner & Rothwell, 2003)*. Smaller coils with an approximate intersection size of 1 x 1 cm are available, but rarely used. Another reason that might limit a more or less exact estimation of spatial resolution is related to the issue of current spread to adjacent and interconnected cortical regions. Several studies have demonstrated remote effects via transsynaptic connections after the delivery of TMS pulses. In an elegant study, Ilmoniemi et al. *(1997)* could demonstrate that following single-pulse TMS applied to M1, electrical activation occurs in the cortical tissue directly under the coil with a latency of < 3 ms, in adjacent regions after

10 ms and in homologous regions of the opposite hemisphere after 24 ms. A very recent fMRI study investigating remote effects after premotor cortex rTMS revealed BOLD signal increases in the cortical area underlying the stimulation coil (PMd), but as can be seen from Figure 4.1-4, also in a wide network of sensorimotor regions interconnected with the left PMd (right PMd, bilateral PMv, supplementary motor area, somatosensory cortex, cingulate motor area, left posterior temporal lobe, cerebellum, and caudate nucleus) *(Bestmann et al., 2005)*.

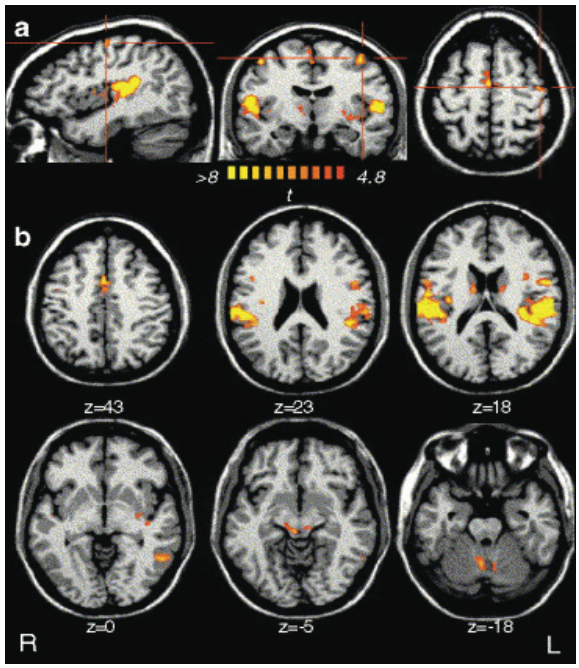


Figure 4.1-4: positive BOLD responses to rTMS (3 Hz, 10 s) applied to the left premotor cortex. (a) activity in the left PMd, (b) activity changes in the cingulate gyrus, PMv, auditory cortex, caudate nucleus, left posterior temporal lobe, medial geniculate nucleus, and cerebellum with coordinates indicated. *(Figure taken from Bestmann et al., 2006)*

Single-pulse TMS can provide very good temporal resolution. Many former studies have used single-pulse TMS in order to obtain information on the timing of cortical processing *(Praeg et al., 2005; Sack et al., 2006)*. The possibility to apply a single TMS pulse with a high temporal accuracy enables to study the contribution of certain cortical regions at particular times during task performance. Schluter et al. *(1998)* followed that strategy and revealed differential effects of TMS stimulation applied to motor and premotor areas. While stimulation of the PMC resulted in impaired movement performance when applied about 140ms after a cue to move, M1 stimulation led to effective impairment about 40ms later. However, in case of single-pulse TMS as it is used in study 1 of this thesis temporal resolution is largely irrelevant.

4.1.6 TMS safety issues

When applying TMS in humans, particular safety issues have to be taken into consideration, especially in the case of repetitive TMS techniques. The major risk of TMS is the induction of epileptic seizures. Until now, only very rare cases have been reported, all limited to rTMS at high frequencies and intensities. However, with patient populations there is a potential risk of seizure induction even with single-pulse TMS. Nevertheless, risks can be largely minimized by carefully selecting subjects and, even more importantly, by following strict safety guidelines. Within these guidelines seizures have never been induced in normal subjects without a family history of epilepsy *(Pascual-Leone et al., 1993; Wassermann, 1998)*. Safety or side-effect concerns also include hearing impairments, hormonal changes, mood changes and cognitive changes *(Cracco et al., 1999)*. However, there are generally much fewer concerns about safety issues with single-pulse TMS. Although there is no evidence for adverse side effects of TMS on brain function *(Bridgers, 1991; Cracco et al., 1999)*, several studies reported favoring effects of rTMS applied to the prefrontal cortex in depressed patients indicating potential long-term effects under special circumstances *(Pascual-Leone et al., 1996)*.

In study 1 of this thesis (see ▸Section 6) single-pulse TMS was used. The frequency and intensity of stimulation used was well within the safety limits recommended by the International Federation of Clinical Neurophysiology.

4.2 Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging belongs to the group of neuroimaging technologies that aims to measure brain function, and therefore explores the relationship between activity in certain cortical and subcortical areas and cognitive functions or motor behavior. Technical advances, particularly during the last decade, now enable optimized signal strength and a strikingly high spatial resolution of less than a millimeter.

4.2.1 Underlying principles

Magnet Resonance Imaging (MRI) is based on the physical principle of nuclear magnetic resonance (NMR) referring to a phenomenon that occurs when atomic nuclei enter a static field with a second oscillatory magnetic field applied.

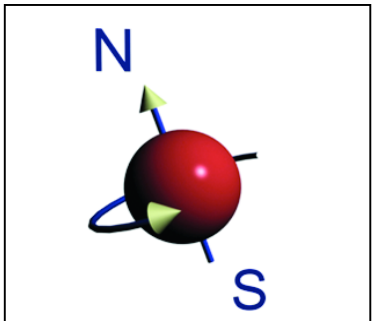


Figure 4.2-1: Schematic proton spin.

Atomic nuclei having an odd number of protons possess a spin (see Figure 4.2-1), which causes them to precess at a particular frequency (Lamor frequency; see below) when subjected to a static magnetic field. The precession movement produces a small magnetic field resulting in a magnetic moment of the proton. MRI exploits the high concentrations of hydrogen nuclei in water present in the human body. The nucleus of a hydrogen atom contains a single proton; hence, the proton

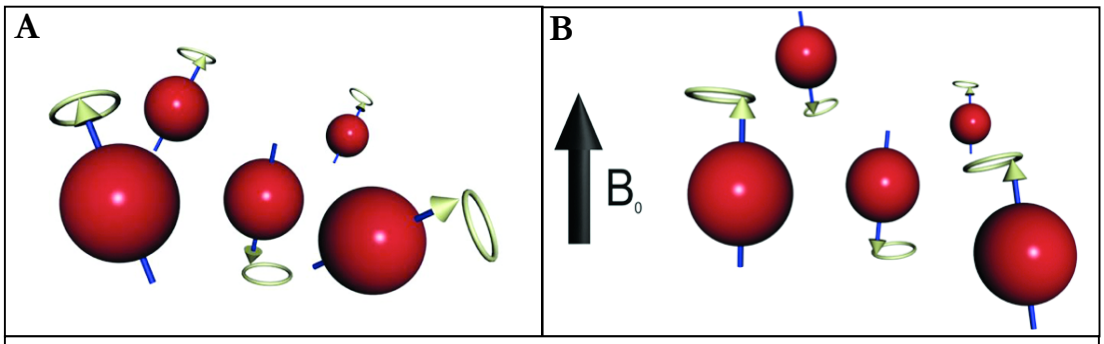


Figure 4.2-2: (A) Random orientation of the proton spins outside a static magnetic field and (B) alignment of proton spins when placed into a static magnetic field *(Images 4.2.-1 and 4.2-2 by courtesy of D. Eicke).*

possesses a significant magnetic moment. Normally, the axes of rotation of hydrogen spins are equally distributed and the net magnetization accounts to zero (Figure 4.2-2 A). When a strong external magnetic field (B_0) is applied, the hydrogen spins align in the magnetic field (Figure 4.2-2 B). Since more hydrogen spins align parallel instead of anti-parallel to the magnetic field, as this is the lower energy state, net magnetization along the static field is larger than zero.

The alignment of protons cannot be completely parallel to the lines of B_0 because of the angle resulting from the precession movement. The precession frequency (= Lamor frequency, ω_0) is dependent on the magnetic field strength (B_0) and the gyromagnetic ratio (γ) of the proton.

Lamor Frequency: $\omega_0 = \gamma B_0$

When transmitting a radiofrequency (RF) pulse, that exactly matches the Lamor frequency of precessing spins, resonance occurs, meaning that energy is transferred to the spin ensemble.

As mentioned above, magnetization develops from the divergent number of parallel and anti-parallel aligned hydrogen spins precessing equally around the lines of B_0. This magnetization in z-direction is referred to as M_z or *longitudinal magnetization*. Compared to the strength of B_0, M_z is too small to be detected. A second magnetization component, orthogonal to the lines of B_0 and orthogonal to M_z, is called *transversal magnetization* M_{xy}. M_{xy} equals zero when the hydrogen spins are placed into B_0 because they precess with different phases and magnetic moments cancel each other out.

The application of an RF pulse provides the spin ensemble with energy causing the single spins (and accompanying M_z) to flip away from z-direction. This excitation happens because some low-energy protons absorb energy and therefore pass to the high-energy level with anti-parallel alignment to the lines of B_0 (= spin flip). The angle by which the spins are flipped depends on the characteristics of the RF pulse. A 90° pulse, for instance, will flip the net magnetization vector into the plane perpendicular to the direction of the static field (the x-y plane). By causing an adjustment of occupation of the two energy levels, the RF

pulse leads to a decline of M_z while net magnetization in the transversal plane generates an electrical signal in surrounding receiver coil. Since the application of the RF pulse causes a phase coherence of the precession movement, magnetization vectors do not cancel each other out anymore, but sum up instead. This way transversal magnetization develops. However, the static magnetic field tries to flip proton spins back to z-direction, thus proton spins precess in the transversal plane around the z-axis. The precession movement of this magnetization vector induces alternating voltage in the receiving MR coil with the frequency identical to the Lamor frequency. This signal is the basis for magnetic resonance imaging. Its decay is influenced by internal and external disturbances of the spin ensemble following a specific time constant (*Free Induction Decay, FID*).

After an RF pulse, two separate processes occur. There is a recovery of longitudinal (z) magnetization and there is decay in transverse (x-y) magnetization. *Longitudinal relaxation* refers to the process of protons back-flipping to the z-direction along B_0 accompanied by giving up energy to surrounding tissue. The time constant describing this recovering of M_z is called T1. *Transversal relaxation* describes the loss of M_{xy} due to a de-phasing of precessing hydrogen spins. Phase coherence present following RF pulse transmission is lost and magnetization vectors again start to cancel each other out. This process leads to a decrease in MR-signal, and finally to a complete signal decay. Energy is not passed to the surrounding tissue rather an energy exchange between spins occurs. Two processes contribute to the signal decay. First, the spin-spin energy exchange induces local fluctuating changes in magnetic field, therefore leading to differences in precessing (Lamor) frequency, which is directly related to the strength of the magnetic field. As a matter of course these local magnetic changes cause the spin de-phasing. The associated time constant is T2. Second, constant inhomogenities, caused by the MR machine itself or by the subject's body, also contribute to the process of spin de-phasing. Given these additional factors, the signal decays not with T2 but with a faster T2*. T1 and T2/T2* relaxation are completely independent processes. While the signal decays already after 100

– 300ms due to the T2* relaxation, it takes about 0.5 – 5 s until M_z has completely recovered.

4.2.2 MR image contrast

The brightness of a certain tissue in the MR image is defined by 3 tissue-specific parameters. *Proton density*, as defined by the number of spins per volume that can be excited, specifies the maximum signal of a particular tissue. The *T1 time* defines how fast spins can recover from stimulation, while the *T2 time* defines how fast the MR signal decays after stimulation. Depending on which parameter is pronounced by the MR recording sequence, images with different tissue-to-tissue contrasts result.

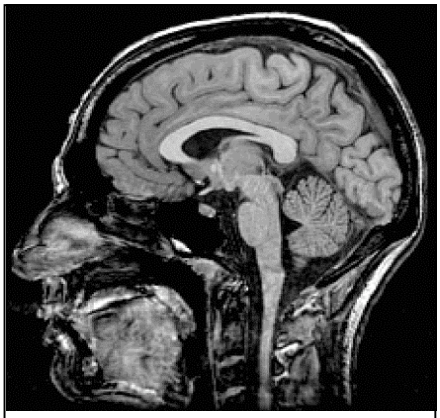


Figure 4.2-3: Midsaggital plane of a T1-weighted anatomical image volume. *(image data from study 3 of this thesis)*

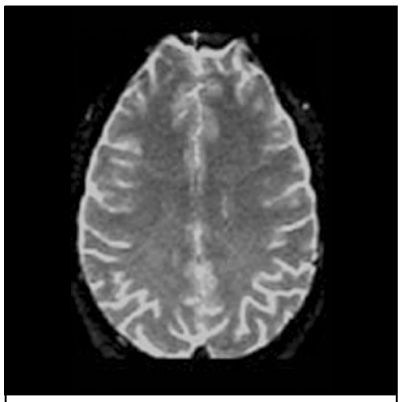


Figure 4.2-4: Horizontal slice of a T2*-weighted functional MR image volume. *(image data from study 3 of this thesis)*

The repetition time (TR) strongly influences the T1-contrast. At a short TR (< 600ms) T1 defines the image contrast. Tissues with short T1 show fast relaxation providing much signal with renewed stimulation (they look bright in the MR image). In contrast, tissue with long T1 relaxes much slower and cannot provide as much longitudinal magnetization at renewed stimulation (they appear less bright). Using a long TR (>1500ms) gives all tissues enough time for relaxation, thus T1-weighting is minimized.

The echo time (TE), which refers to the time interval between stimulation (RF pulse) and signal detection, determines the T2-weighting of MR images. Given that T2 is much shorter compared to T1, signal intensity changes between tissues are small when using short TE (T2-relaxtion for all tissues has just begun and the signal decay has not advanced much). Thus, T2-weighting is low.

Choosing a longer TE (about 60ms) clearly enhances image contrast. Tissues with short T2 have lost most of the signal and appear dark in the MR image whereas tissues with long T2 still provide some amount of signal and look brighter.

Being more specific with regard to neural tissues, grey matter appears darker compared to white matter in anatomical, T1-weighted images (e.g. TR = 500 ms, TE = 20 ms) (see Figure 4.2-3). In case of functional MR weighting (e.g. TR = 2000ms, TE = 60ms), grey matter appears brighter than white matter due to the larger T2 time of grey matter (see Figure 4.2-4).

In MR imaging, spatial information about the signal source is provided by three orthogonal gradient coils (G_x, G_y, G_z), each of them generating a small spatially varying magnetic field along one axis that is superimposed on the large static magnetic field. Horizontal slice selection (z-axis) is ensured because G_z forces protons at different points along the gradient to precess at different frequencies. Since a particular RF pulse frequency only excites protons of a spatially narrow layer of tissue, the RF pulse is applied at a range of frequencies (bandwidth) designed to flip protons at a particular range of spatial locations along the z-axis. Gradients generated by G_x and G_y allow for spatial coding within a slice. The *phase-encoding gradient* provided by G_y causes protons at different points along the y-axis to precess with a different phase while the *frequency-encoding gradient (provided by G_x)* produces spatial modulations of precessing frequency along the x-axis. The unique precessing phase and frequency of spins within a voxel of a given slice encodes the spatial location of that voxel. The signal from each slice is received in k-space with frequency information being reconstructed into an image by using Fast Fourier Transformation (FFT) algorithms. Meanwhile, echo-planar imaging (EPI) techniques that are commonly used for fMRI enable the sampling of the entire k-space after a single RF pulse.

4.2.3 Physiological basis of fMRI: The BOLD effect

Measuring neuronal activity with MRI requires a contrast in MR signal between resting and activation conditions that can be subjected to further analyses. This

contrast is indirectly represented by metabolic changes coupled to neural activity. In case of specific information processing in neuronal structures, nerve cells become activated and as a consequence an increase of local cerebral blood flow (CBF) is needed to account for the increased requirements of glucose and oxygen (O_2). The exact physiological mechanisms defining the increase in local CBF are still under intense discussion. It has been suggested that the need for glycogen determines the extent of increase in local CBF since the additionally provided glycogen is indeed almost fully used up. In contrast, the actual oxygen demand is clearly smaller than the amount provided by the CBF increase. The induced discrepancy between O_2-supply and O_2-consumption leads to an increase in local O_2 concentration in the capillary veins. One theory that tries to explain the phenomenon of O_2 over-supply suggests that the non-oxidative metabolism plays a role during neuronal activation *(Magistretti et al., 1999)*. The hypotheses of Magistretti and co-workers are based on the evidence that glutamate released at the synapse is taken up by astrocytes which in turn triggers increased glucose uptake from capillaries. The glucose is metabolized glycolytically into lactate, which is then oxidized by neurons. Another model by Buxton et al. *(1998)* (=oxygen limitation model) refers to the fact that O_2 transfer into brain tissue is limited by diffusion from capillaries and depends largely on the O_2 concentration gradient between the vasculature and the tissue. However, it is clear that changes in O_2 concentration influence local magnetic conditions. Oxygenated haemoglobin (oxy-Hb) has diamagnetic properties and does not disturb the magnetic field B_0. Deoxy-haemoglobin (deoxy-Hb), on the other hand, has paramagnetic properties and produces small inhomogenities of the magnetic field close to the deoxygenated blood. Functional MRI exploits changes in the ratio of oyx- and deoxy-haemoglobin. An increased proportion of oxy-Hb on the expense of deoxy-Hb, as it is the case during neuronal activity, leads to reduced magnetic susceptibility around the vessels, and thus higher MR signal due to extended T2* (retarded spin de-phasing process). The resulting contrast in MR signal was first described by Ogawa et al. *(1990)*.

Up to now many studies have attempted to explore how BOLD signal changes relate to underlying electrophysiology. Particular contributions come from Lo-

gothetis and colleagues, who extensively used fMRI and electrophysiologic recordings in monkeys to address this question. Based on their observations of a tight relationship between local field potentials (LFPs) and BOLD signal changes *(for an overview see Logothetis & Wandell, 2004)*, they assumed that the BOLD signal predominantly reflects input and local processing of an area rather than its spiking output. The fact that events at the synapse, such as re-establishment and maintenance of membrane potentials by active ion transport and glutamate reuptake by astrocytes, are much more metabolically demanding than spiking activity itself, lends further support this line of interpretation *(Magistretti & Pellerin, 1999)*. However, there is some evidence that spiking activity is reflected in the BOLD signal as well, although it cannot completely predict the signal.

In general, BOLD signal changes resulting from neuronal activity are small, (~ 2-5%) and although the T2* relaxation rate (and therefore the size of signal) can be increased using a higher field strength, noise and artifacts are also enhanced since they depend on the same principle of magnetic susceptibility as the signal one is interested to measure.

4.2.4 Echo-planar imaging and the SENSE technique

BOLD effects are usually measured using sophisticated echo-planar imaging (EPI) techniques developed by Peter Mansfield *(1977)*. EPI is a very fast and efficient MR imaging technique. In case of single-shot EPI, all the spatial-encoding data of an image can be obtained after a single radio-frequency excitation. The EPI technique describes, strictly speaking, only the method to readout the signal. It can be combined with different excitation schemes and manipulations of the transversal magnetization. Besides performing the readout during the Free Induction Decay (during gradient-echo EPI sequences, GE-EPI), the Signal acquisition is also possible during a spin echo, which is generated by a second excitation pulse as in spin-echo EPI sequences (SE-EPI). The use of SE-EPI sequences reduces large vessel effects ("Brain or Vein" – "Oxygenation or Flow" problem) since they have a lower sensitivity in detecting larger blood vessels. Unfavorably, however, SE-EPI compared to GE-EPI sequences are

also less sensitive to the BOLD signal, which goes along with a higher detection uncertainty regarding the hemodynamic response. GE-EPI sequences, on the other hand, are prone to severe susceptibility artifacts. Furthermore, the spatial resolution strongly depends on timing restrictions on optimal BOLD weighting (TE = 35ms).

The study reported in ▸Section 8 combined standard single-shot GE-EPI with sensitivity encoding (SENSE) in order to ensure sufficiently high spatial resolution and a good signal-to-noise ratio at a field strength of 3 Tesla. The SENSE imaging technique has been developed and first published by Pruessmann et al. *(1999)* and refers to a parallel imaging technique that allows for higher encoding efficiency, and thus for faster data acquisition and / or higher spatial resolution *(for technical details see Pruessmann et al., 1999)*.

4.2.5 Spatial and temporal resolution of fMRI

The actual spatial resolution of a study is determined by factors including contrast to noise, amount of motion, the contribution of large vessel effects, and the location and extent of metabolic and hemodynamic changes that occur with neuronal activation. Locally increased blood flow at sites of neuronal activity typically reflects increased metabolic demand at the synapses. As mentioned above, Magistretti & Pellerin *(1999)* suggested that glutamate reuptake by astrocytes surrounding synapses may be a major component of the metabolic demand. To enhance spatial resolution, it is currently discussed to restrict functional MR imaging to the initial dip of the BOLD response that is thought to correspond to an early increase in oxygen extraction during neuronal activation when the increase in CBF has not yet occurred *(Vanzetta & Grinvald, 1999)*. Even though this technique seems to provide promising results it depends on very high magnetic field strength and fine temporal resolution. An alternative approach has been applied in an elegant study of ocular dominance columns in human subjects *(Menon et al., 1997)*. Visual stimulation of the left or the right eye activated overlapping voxels in visual cortex; but identifying those voxels that were activated more by left than right eye stimulation and vice versa the authors were able to map out interleaved ocular dominance columns.

In order to meet the high spatial resolution demanded in study 3 of this thesis, we refrained from whole head scanning and decided to limit data acquisition to 6 transverse slices (covering the hand motor area) on the advantage of high-resolution SENSE encoded single-shot EPI. This resulted in an effective in-plane voxel size of less than a millimeter.

With respect to the temporal resolution one has to take into account that the effect inherently measured by fMRI is very slow. In principle temporal resolution of this method can be very high as fMRI can be acquired in tens of milliseconds; for example on a 3T MRI system, a two-dimensional image with a size of 64 x 64 pixels can be recorded in ~30ms. However, the hemodynamic response (hrf), which is the physiologic basis of BOLD imaging, typically peaks at about 4-6 seconds after the onset of a stimulus. Hence, the temporal resolution of fMRI is poor relative to the electrical signals that define neuronal communication. Therefore, at present, much research effort is dedicated to the issue of combining fMRI with data acquisition techniques such as electroencephalography (EEG) that can provide a much higher temporal resolution. Analysis is further complicated by the fact that temporal hrf characteristics have shown to vary between individuals, cortical areas and tasks *(Aguirre et al., 1998; Rajapakse et al., 1998)*. In practice, temporal resolution is largely dependent on the repetition time (TR). Given that it is preferable to allow enough time for the tissue to recover longitudinal magnetization, the TR should be longer than T1 (at least 1- 1.5 seconds). Hardware properties of the MR scanner, e.g. the capacity for rapid gradient switching, also play a role in limiting the temporal resolution.

As we were not interested in addressing temporal characteristics of the BOLD response in case of the study reported in ▸Section 8, a conventional powerful block design was used with task blocks of 20 seconds duration alternating with baseline blocks. Hence, temporal resolution was not a critical issue here.

4.2.6 Image analysis

This section provides a short overview of the processing steps that have been followed in study 3 of this thesis to calculate statistical maps from raw fMRI data. Image analysis was performed on a PC using SPM2 (*http://fil.ion.ucl.ac.uk/spm*) running on MATLAB 5.3 (*Mathworks Inc., Natiek, MA, USA*).

4.2.6.1 Preprocessing of FMRI data

Motion correction (realignment). Movement of the brain within the imaged space cannot be completely avoided during the course of an fMRI experiment. Obvious motion caused by the subject itself contributes as well as physiological factors (e.g., the cardio-respiratory cycle). This movement may cause that the signal provided by a certain voxel does not correspond to the same brain location across the measurement *(Friston et al., 1995)*. In the experiment presented in ▸Section 8 linear image registration techniques are used (implemented in the SPM2 software) to align all recorded volumes to the first volume of the time series.

Spatial normalization. There is large interindividual variance in brain morphology. Spatial normalization procedures reduce variance and enable the comparison of data from corresponding regions of individual brains, therefore providing the basis for interindividual comparisons. All acquired MR images become coregistered to a standard reference space. The most common reference brain is provided by the Montreal Neurological Institute (MNI) and is based on 300 individual brains. The idea is to ensure that single anatomical structures occupy the same voxel in each individual. SPM2 estimates the exact transformations necessary for a brain to be transferred into reference space following the rule of least deviation squares *(Friston et al., 1995; Ashburner & Friston, 1999)*. Normally, SPM2 uses affine as well as non-linear transformations enabling global scaling (enlargement, size reductions), rotation and displacement, but also local distortions to ensure optimal fit to the template. In a second step the extracted parameters are applied to all images.

Because one of the interests of experiment 3 was to reassess the issue of fine-scale arrangement of finger representations with respect to the homuncular idea, we performed a transformation of individually determined COM coordinates into stereotaxic reference space, however, restricting normalization to linear algorithms.

Spatial smoothing: The main reason for applying a smoothing kernel to the fMRI data is to increase the signal to noise ratio. The underlying idea is the following: noise that varies randomly from voxel to voxel should be cancelled out by spatially smoothing. However, does the extent of neuronal activity exceed the size of the smoothing kernel, activation should survive the smoothing procedure. Thus, spatial smoothing reduces the spatial resolution of the data, but at the same time minimizes influences of stochastic errors. Applying a smoothing kernel is also necessary to adjust data according to the Gaussian Field model which underlies statistical conclusions at further data analysis assuming that the data are spatially smooth.

In study 3, spatial smoothing has been performed using a very small Gaussian kernel of 1.5 mm at full width at half maximum to maintain the high data resolution.

4.2.6.2 Statistical analysis of single subject FMRI data

Statistical modeling: Once the data preprocessing has been finished, statistical analyses aim to assess whether experimental manipulation has induced reliable changes in fMRI signals and where those changes occur. There are a number of statistical approaches to quantify the correspondence between data and task paradigm. In study 3 of this thesis the signal time course from each voxel was compared to the expected hemodynamic response (the box car function convolved with a hemodynamic response function) in the framework of the general linear model (GLM).

The GLM is a statistical, linear model that can generally be written as

$$Y = XB + \varepsilon$$

where **Y** is a matrix with series of multivariate measurements, **X** is a matrix that might be a design matrix, **B** is a matrix containing parameters that usually have to be estimated and **ε** is a matrix containing residuals (i.e., errors or noise). Regarding functional MRI, the GLM is used to describe the variability in the data (**Y**) in terms of experimental and confounding effects (**X**), and residual variability (**ε**). Hypotheses expressed in terms of the model parameters are assessed at each voxel with univariate statistics. That way, statistical parametric maps of the T-statistic are created.

After the calculation of statistical maps it becomes necessary to decide which voxels represent significant activation. Since the statistical parameters of each voxel are associated with a probability (p-value), this information can directly be used for thresholding. However, the high number of voxels included in the image space (which define the number of statistical tests that have to be conducted) results in a strongly increased risk for type-1-errors (false positives). This is commonly known as the problem of multiple comparisons. Given that the voxels are not independent of one another, applying Bonferroni corrections would be too conservative. Alternatively, more lenient adjustments are made based on the theory of continuous random fields. Please refer to ▸Section 8.5 to find detailed information about data analysis that was performed in study 3 of this thesis.

As mentioned above, study 3 exploits the advantages of a conventional, statistically powerful block design. The high efficiency enables the collection of reliable data in a short time; reducing subjects' discomfort and motion artifacts which is a particularly important issue given the very high spatial resolution.

4.2.6.3 Multi-subject statistics

The majority of fMRI experiments was planned to investigate brain activation patterns for a particular population, or task, or differences between them. After transferring the individual brain to standard reference space,

statistical analyses can be conducted to assess brain activation or activation differences. Fixed effects analyses only consider within-subject variance whereas a random effect analysis additionally considers between-subject variance. Since results from experiment 3 are exclusively based on the region-of-interest (ROI) approach, traditional group analyses will not be issued here. In general, ROI analyses are based on anatomically defined regions of interest that are, in case of the present study, drawn on individual high-resolution scans. Statistics are then computed within ROIs. It is important to note that ROIs from different subjects do not have to overlap in standard brain space, thus interindividual differences are taken into account. The ROI approach is particularly indicated to test a-priori hypotheses for precise brain regions. Hence, the correction for multiple comparisons must not be carried out for the entire brain, which provides more statistical power. For a detailed description of the ROI analysis please refer to ▸Section 8.5.

4.2.7 Safety of MRI

No serious side effects of being in an MRI scanner have been reported after more than twenty-five years of use. The major safety concern with the main magnetic field refers to the risk of moving metal objects. These metal objects could be small objects such as pacemakers or metal implants. Such conditions are generally considered an absolute contraindication towards MRI scanning. In case of metal body implants that are not ferromagnetic there still is the risk of thermal injury from radiofrequency induced heating of the object.

Claustrophobia as a psychological reaction to being confined in a relatively small area is a very real psychological danger for some individuals during MRI. A small percentage of patients is claustrophobic and cannot tolerate the confined space within a closed MRI magnet.

Forces resulting from rapidly switched magnetic gradients interacting with the main magnetic field produce loud noises and vibrations. The sounds made by the scanner vary in volume and tone with the type of procedure being performed. The noise is generally most marked with high-field machines and rapid-

imaging techniques in which sound intensity can reach 130 dB. By using disposable earplugs and/or headphones serious health risks can be eliminated.

4.3 Electroencephalography (EEG)

Electroencephalography refers to the neurophysiologic measurement of electrical brain activity by recording from electrodes placed on the scalp. The resulting traces are known as an electroencephalogram and represent so-called brainwaves. In 1924, first EEG recording in man was accomplished by Berger who referred to it as *Electroenkephalogram (Hans Berger, 1929: Über das Elektroenkephalogram des Menschen)*. Using the EEG he was also the first to describe the different waves or rhythms which were present in the normal and abnormal brain, such as the alpha wave (also known as Berger's wave). The EEG provides information about the time course of the neural firing and allows inferences on the underlying brain activity using an appropriate inverse solution.

Usually, the internationally standardized *10-20 system (→ American Electroencephalographic Society guidelines for standard electrode position nomenclature, 1991)* is employed to record the spontaneous EEG. In addition to the 21 electrodes of the international 10-20 system (displayed in Figure 4.3-1), intermediate 10% electrode positions are also used in many studies.

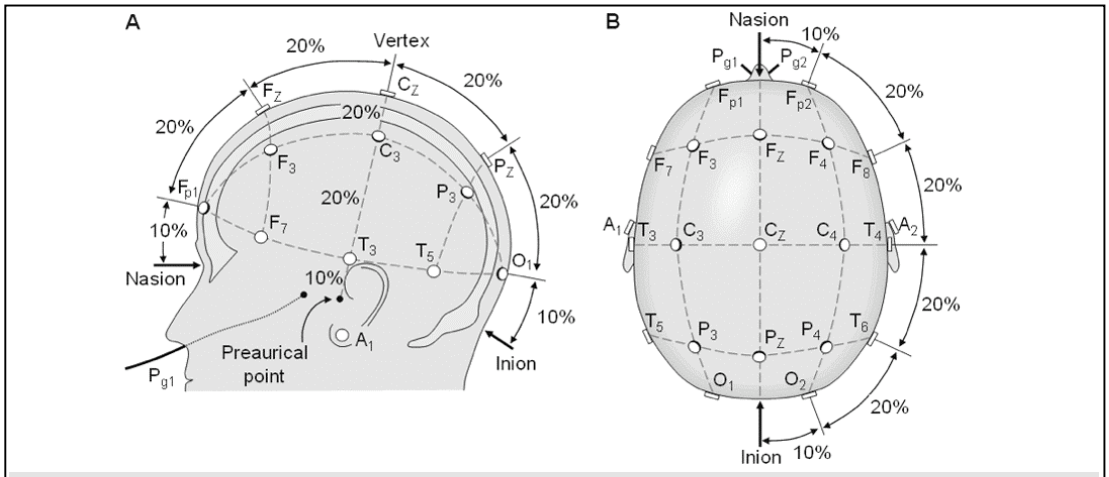


Figure 4.3-1: The international 10-20 system seen from (A) left and (B) above the head. *(Modified from Sharbrough et al., 1991)*

4.3.1 Physical principles

In his early work, Berger *(1929)* found small changes in voltage between two electrodes when placed on the scalp. The exact physiologic basis of the voltage variations is not entirely known, but it is believed that EEG scalp electrodes pick up electrical potentials created by large groups of neurons that fire in synchrony. This section aims to elucidate the electrophysiological basis of the EEG signal recorded at the scalp.

Understanding EEG requires understanding of the sources of electrical activity in the cortex and the reasons for the constant rhythmical oscillations in polarity and amplitude. Neural signaling – the basis of brain function – relies on a complex interplay of ionic currents. Synapses represent the nodes of neural signaling. On average, the axon of a neuron builds synapses to about thousand other neurons. By releasing neurotransmitters into the synaptic gap, signals are transferred from one neuron to a second one, where an excitatory or inhibitory postsynaptic potential (EPSP / IPSP) is elicited. These postsynaptic potentials (PSPs) are important for the measurement with EEG. Because of having larger amplitudes and being more numerous than IPSPs, EPSPs are suggested to be the primary contributors to the signal recorded with scalp EEG. The release of neurotransmitters at the synapse leads to selective movements of ions through the postsynaptic membrane, resulting in local changes of ionic concentrations intra- and extracellularly and thus forming a dipole. By definition, a current dipole consists of a source and a sink. Induced extracellular ionic currents give rise to voltage differences recorded at scalp electrodes.

Pyramidal cells in the cortex are likely to be the primary neural source of EEG. As their apical dendrites are long and arranged in parallel (pointing perpendicularly to the surface of the cortex), PSPs can develop in one part while remote parts compensate with opposite behavior, thus forming the afore-mentioned dipoles. In other words: When an EPSP occurs at a dendrite site remote from the soma (close to the surface) it leads to a local inflow of positive current into intracellular space leaving negativity in local extracellular space. This negativity in turn attracts positive ions from surrounding areas, including superficial ones.

Thus, due to this deficit of positive charges, the surface electrode detects negativity. Individual PSPs are too small to be detected by surface electrodes; however, there are several hundreds of thousands synapses in the recording space of a surface electrode. Temporal synchrony of synaptic activity, and therefore synchrony of many thousand PSPs, leads to the summation of the neuronal activity (spatial and temporal overlapping of thousands of dipoles) which then becomes visible for scalp EEG. The resulting voltage amplitudes recorded at the scalp are small, typically in the range of microvolts.

Generally, one can dissociate induced and spontaneous brain activity measured with EEG. The term 'induced brain activity' refers to certain types of stimulus-related activity (= stimulus-related voltage changes). These so-called evoked potentials (EPs) or event-related potentials (ERPs) are obtained from the raw EEG signal by stimulus-locked averaging. As a consequence, the signal components that are identical in response to each stimulus (event) are conserved while the spontaneous neural activity is canceled out. In contrast, the term 'spontaneous' (or 'ongoing brain activity') refers to components of the EEG signal that are not directly related to the processing of a specific stimulus or event. Since the EEG study included in this thesis (see ▸Section 7) is based on spectral analysis of ongoing brain activity, we will focus on quantitative EEG techniques in the following sub-sections.

4.3.2 Spontaneous EEG

The concept of neural oscillations is close to the concept of brain waves. The idea of brain waves however usually refers to scalp EEG recordings whereas the conceptualization of neural oscillations has been rather linked to more invasive recording techniques using electrodes directly contacting the brain (e.g., extra- and intracellular single-unit recordings or recordings of local field potentials). Neuronal oscillations represent a typical characteristic of brain cells and neural ensembles; but the physiological basis for oscillatory EEG behavior is still poorly understood. Brain oscillations occur at different frequency ranges, but there is no precise agreement on the frequency ranges for each type of oscil-

lation. In general, brain waves are thought to arise from the oscillation of post-synaptic potentials in the cortex.

Low frequencies as *delta* (1.5-6 Hz) and *theta* (6.5-8 Hz) have been suggested to indicate functional inhibition. These oscillations have been shown to dominate during sleep in healthy adults. Some studies suggested increased slow wave activities during focused attention or conditions of meditation *(Aftanas & Golocheikine, 2002; Kjaer et al., 2002)*. On the other hand, untypical amounts of slow-wave activity in adults can indicate pathological processes.

An oscillatory component is defined by the presence of a rhythmic activity in the EEG that is manifested by a peak in spectral analysis. The classical parieto-occipital *alpha* waves (8-13Hz) clearly meet these criteria. Alpha waves predominate in ongoing EEG during a state of relaxed alertness in most young adults (~95%) and occur as a pattern of regular, sinusoidal electrical oscillations, mainly over parieto-occipital areas. The German Neurologist Hans Berger was among the first to describe the *occipital alpha rhythm* and the associated phenomenon of the so-called *alpha blockade* that refers to the suppression of alpha oscillations when the subject opens the eyes. A great variety of rhythms within the broad alpha frequency band exists that can be distinguished by their topography and response patterns to certain events. Besides parieto-occipital alpha rhythms, central *mu* oscillations have been extensively studied *(Pfurtscheller et al., 1997)*. In addition, the so-called *tau* rhythm has been reported to occur over the midtemporal region *(Tiihonen et al., 1991)*. The particular properties of the *mu* rhythm will be discussed in ▸Section 4.3.3 since this rhythm has been studied in study 2 of this thesis.

Brain waves in the *beta* frequency range (13–30 Hz) appear to be dominant during the state of active wakefulness. Low amplitude beta with multiple and varying frequencies is often associated with functional excitation and intense mental activity. However, there is strong evidence that functional properties of beta waves change in dependence of the underlying brain region. In the motor domain, *beta* activity is suppressed when movement occurs – a finding that contradicts with the idea that beta activity reflects functional excitation. It has specifi-

cally been shown that *beta* desynchronizes in preparation and following voluntary hand movements *(Pfurtscheller et al., 1998; Neuper & Pfurtscheller, 2001)*, but also during mere perception of movement *(Cochin et al., 1998)*.

4.3.3 The mu rhythm

The *mu* rhythm refers to an EEG oscillation that is most prominent at electrodes overlying the sensorimotor cortex in the absence of movement *(for a review see Pineda, 2005)*; attenuated with voluntary movements, motor imagery, observation of movements or somatosensory stimulation. It is also known as the central, Rolandic, sensorimotor, wicket, or arceau rhythm. There are several contrary reports on the mu frequency in former literature *(Kuhlman, 1978; Stancak, Jr. & Pfurtscheller, 1996)* that give rise to the conclusion that the *mu* frequency seems to cover a broad frequency range between 7 and 15 Hz with a mean frequency of about 10 Hz. However, recent work has provided evidence for the existence of several *mu* sub-rhythms with slightly differing peak frequencies and associated differences in the functional response pattern. *Mu* oscillations are limited to brief periods of 0.5 to 2 s duration (see Figure 4.3-2). In analogy to the classical parieto-occipital alpha waves, the *mu* rhythm has been interpreted as reflecting a state of cortical 'idling'. It is particularly evident when the motor areas are not generating motor outputs.

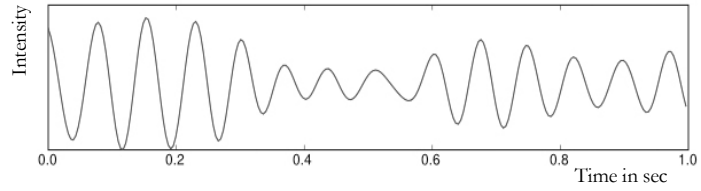


Figure 4.3-2: The sensorimotor *mu* rhythm.

With respect to voluntary limb movements, Pfurtscheller et al. *(2000)* provided evidence for functionally dissociable lower and upper frequency *mu* rhythms. The lower frequency *mu* rhythm (8-10 Hz) shows a widespread, rather non-specific desynchronization with movement. In contrast, the upper frequency *mu* rhythm was linked to more focused movement specific desynchronization,

clearly different with finger and foot movement. Hand movements led to upper *mu* rhythm desynchronization at central contralateral electrodes (C3 / C4) while this contralateral preponderance was not present with foot movements.

4.3.4 Spectral analysis of spontaneous EEG

The most common way to analyze spontaneous, ongoing EEG is its transformation into the frequency domain by means of Fast Fourier Transform (FFT) algorithms, assessing spectral power in certain frequency bands of interest as well as intra- and interhemispheric coherence. One fundamental way to quantify electrophysiologic changes linked to a certain event or task is to calculate percentage changes between spectral power values obtained during the activation and a reference period. This approach is described in detail in the following two sections.

4.3.4.1 Event-related desynchronization / synchronization

Classical examples of event-related desynchronization are (1) the blocking of the parietal-occipital alpha rhythm and (2) the blocking of the sensorimotor and beta rhythms with movement. About 30 years ago, Pfurtscheller & Aranibar *(1977)* introduced a method to quantify event-related desynchronization by comparing power values obtained from a pre-stimulus reference period with those obtained in response to a stimulus or event (= active period). The classical equation that was used by Pfurtscheller et al. to determine the event-related percentage of power decrease (ERD) or increase (ERS) is given below *(Pfurtscheller & Aranibar, 1977; Pfurtscheller & Aranibar, 1979)*:

$$ERD\% = \frac{SpectralPower_{REFERENCE-Period} - SpectralPower_{ACTIVE-Period}}{SpectralPower_{REFERENCE-Period}} * 100$$

Note that, using this particular equation, ERD (reflecting relative power decrease) is expressed by positive values while negative values indicate ERS (reflecting relative power increase). In later publications the original

equation has been changed to make sure that power increase is linked with positive values:

$$ERD\% = \frac{SpectralPower_{ACTIVE-Period} - SpectralPower_{REFERENCE-Period}}{SpectralPower_{REFERENCE-Period}} * 100$$

The appropriate selection of frequency bands is among the most critical issues when using ERD to reveal changes in induced band power. Because of its importance, this issue will be discussed in detail below (see ▸Section 4.3.5).

One example for the time course of a movement-related ERD is shown in Figure 4.3-3 *(Neuper & Pfurtscheller, 2001)*. Subjects performed simple movements of the right index finger. Two important findings are indicated: (1) the central ERD started earlier contralateral to the moving hand and (2) ERS is evident at posterior electrode positions. This has been thought to reflect suppressed information processing at sides not involved in motor performance and enhanced processing capabilities in the hand motor regions.

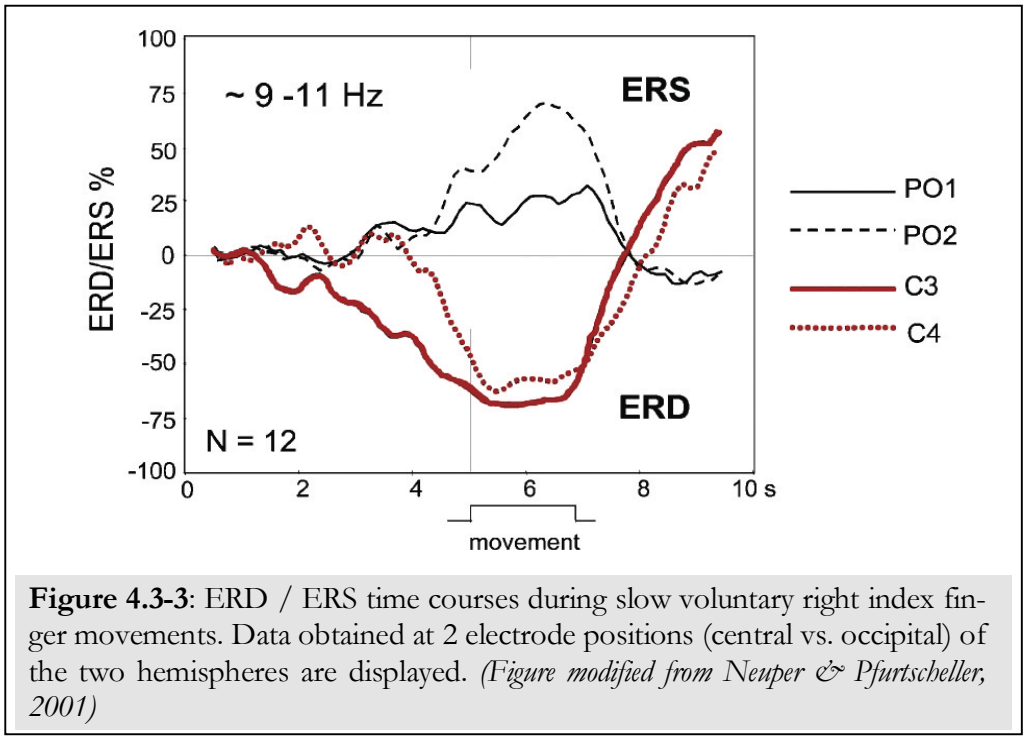


Figure 4.3-3: ERD / ERS time courses during slow voluntary right index finger movements. Data obtained at 2 electrode positions (central vs. occipital) of the two hemispheres are displayed. *(Figure modified from Neuper & Pfurtscheller, 2001)*

The approach of event-related desynchronization directly serves to explore neural events that follow a single event or stimulus. However, this approach does not apply when studying steady-state task performance instead of single events. Therefore, Gerloff et al. *(1999)* have introduced an adapted approach that is based on the early idea of ERD/ERS. To emphasize that the resulting activation patterns relate to task performance rather than to single events, the authors referred to it as *Task-Related Power Change*. Task-related power increases (TRPI) would correspond to ERS, while task-related power decreases (TRPD) would comply with ERD. Study 2 of this thesis was designed to study fast, repetitive tapping movements that are carried out at a movement frequency of up to 6 Hz. Given that single motor responses were spaced too closely in order to define single, analyzable events, this study was preferentially based on the approach of TRPD/TRPI.

The calculation of TRPD / TRPI is accomplished in several main steps:

i. Digital filtering of the raw EEG data (e.g., 1 - 30 Hz)

ii. Segmentation of the filtered EEG data into non-overlapping short epochs (e.g., 1 or 2 sec)

iii. Application of Fast Fourier Transform (FFT) algorithms to all EEG sweeps and electrodes and extraction of spectral power values for all frequency bins in the range defined in the beginning (i)

iv. Averaging of the power spectra for the different experimental conditions

v. Calculation of task-related spectral power (for a given frequency band of interest) by subtracting power levels at a reference period from those obtained during the active task period

4.3.5 The issue of individually defined frequency bands

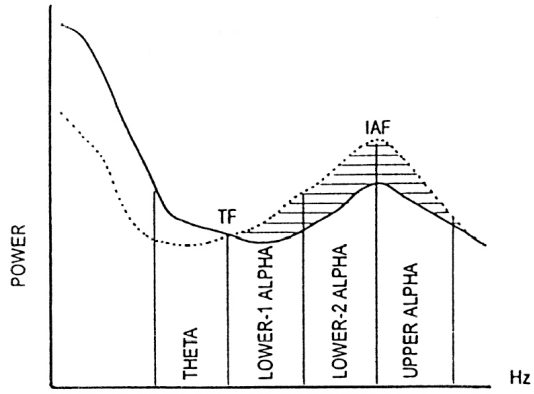


Figure 4.3-4: Individually defined frequency bands in relation to the IAF. Lines indicate calculated power spectra during relaxed alertness [dotted line] and memory task performance [solid line]. *(Figure taken from Klimesch et al., 1999)*

The majority of studies investigating brain function by means of spectral EEG power or coherence have based their analysis on classically defined frequency bands. However, some groups have questioned whether classical frequency bands provide a useful description of the EEG signal. Klimesch et al. *(1999)* was among the first who suggested the use of individually defined frequency bands. It is known that the individual alpha frequency (IAF), which is the frequency showing the largest power in the alpha-spectrum approximately between 7 and 13 Hz, varies as a function of age, brain volume but also cognitive performance or neurological diseases. Even in a sample of age-matched subjects there is considerable variance with respect to the IAF (9.5 – 11.5 Hz in healthy young adults). Klimesch therefore used the IAF as an anchor point to define frequency bands individually for each subject. He defined 3 different frequency bands that are displayed in Figure 4.3-4. However, most studies that have been using IAFs for spectral analysis of brain activity have been carried out in the context of cognitive tasks performance (e.g., memory tasks). In contrast, study 2 (reported in this thesis) investigates motor behavior, thus, the sensorimotor (mu) rhythm was focused. Given that the IAF is less pronounced, and thus more difficult to detect at central electrode sites overlying M1/S1 compared to occipital sites, a different approach was chosen in the present work. The identification of dominant individual alpha frequencies (mu frequencies) in the motor domain was accomplished on the basis of the frequency showing most prominent differences in power between a resting baseline and an averaged movement condition. This approach was chosen be-

cause it is not yet clear whether the dominant alpha frequency is constant across different functional cortical systems.

4.3.6 The functional significance of alpha rhythms

Several studies have aimed to explore functional properties of the alpha rhythms by means of neuroimaging techniques such as fMRI or PET. Simultaneous recording of EEG and fMRI has only recently become possible. Laufs et al. *(2003)* have studied brain activation changes related to spontaneous modulations in the alpha rhythm. As shown in Figure 4.3-5, they reported a strong negative correlation of parietal and frontal cortical activity with alpha power. Another study by Goldman et al. *(2002)* revealed a negative correlation between BOLD signal and alpha power in regions of occipital, inferior frontal, superior temporal and cingulate cortex. Thus, in summary, these two studies provide support for the hypothesis that increased alpha activity corresponds to decreased functional activation in the underlying cortex. Findings from earlier studies using simultaneous PET and EEG support the dominant negative correlation between alpha power and activity in the occipital cortex *(Sadato et al., 1998; Danos et al., 2001)*. With respect to the motor cortex, however, previous studies provided an inconclusive picture, showing either a positive, a negative or no relation *(Buchsbaum et al., 1984; Sadato et al., 1998; Larson et al., 1998)*. Conflicting results have been also reported for the thalamus. Given that parts of the thalamus are suggested to be involved in the synchronization of alpha rhythms, correlations of alpha activity and brain metabolism are of great relevance in this structure. While negative correlations have been reported in some studies *(Larson et al., 1998; Lindgren et al., 1999)* others provided evidence for positive correlations *(Sadato et*

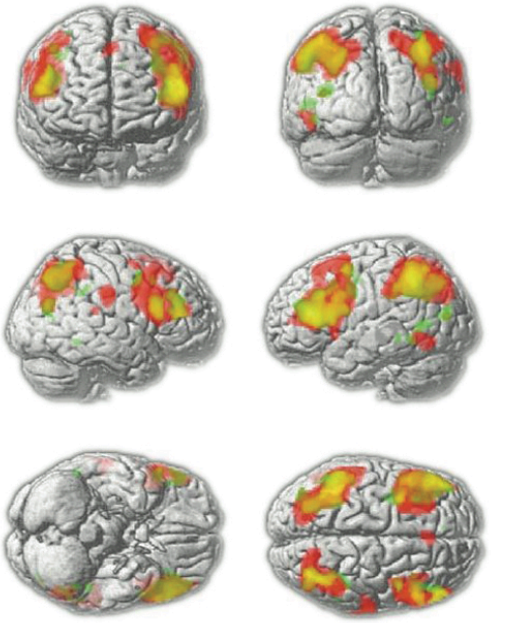


Figure 4.3-5: Cortical Regions showing a negative correlation between alpha power levels and BOLD signal *(Figure taken from Laufs et al., 2001)*

al., 1998; Danos et al., 2001; Goldman et al., 2002). This discrepancy might be attributed to methodological differences between studies. Both, Larson et al. *(1998)* and Lindgren et al. *(1999)* used a PET technique with a particular low temporal resolution of about 30 minutes. Therefore, due to technical limitations, it is not possible to track phasic changes in the EEG signal with PET. As a consequence, the results rather point to trait –like correlations of alpha power and thalamic activity. In contrast, studies by Goldman et al. *(2002)* and Sadato et al. *(1998)* were based on a much better temporal resolution, enabling them to track intrasubject modulations in alpha activity with the respective imaging methods. In conclusion, more studies exploiting simultaneous fMRI and EEG are needed in order to uncover more consistent and reliable relationships between brain oscillations and brain metabolism.

4.3.7 The 'inverse' Problem

The main problem of EEG is to relate electric potentials, as recorded at the scalp, to the intracerebral neuronal sources (i.e., their strength, position, orientation). This problem is referred to as the underdetermined inverse problem, that is, an infinite number of different three-dimensional source distributions could have produced the measured scalp distribution of brain electric activity. The only way to solve this problem is to constrain it.

The simplest constraint to the inverse problem is to assume a single dipole generator source. In order to identify a putative single source an iterative procedure is used. For each possible location and orientation of the single source a feed-forward solution, which is not ambiguous, is calculated. The resulting scalp field distributions are then compared to the measured scalp distribution of brain electric activity. The solution that fits best the measured data identifies the best fitting single model source. For the frequency domain, an adaptation of the source modeling approach - the so-called 'FFT Dipole Approximation' - was introduced by Lehmann & Michel *(1990).* Given that information processing generally takes place within wide, distributed networks, and therefore requires complex cooperation between nearby and remote areas, approaches that identify single dipole sources or trying to fit a small set of dipole models to the

measured data seem inappropriate, especially in cases when there is a lack of assumptions regarding the intracortical source distribution.

Low Resolution Brain Electromagnetic Tomography (LORETA) is a particular 3D, discrete, distributed, linear solution to the inverse EEG problem *(Pascual-Marqui et al., 1994; Pascual-Marqui et al., 1999)*. It will be specifically discussed in the following subsection.

4.3.7.1 LORETA: One solution of the 'inverse' problem

Unlike dipole models, LORETA does not make assumptions on the number of putatively existing dipole sources, but instead directly computes a 3D distributed linear solution for the EEG inverse problem within a three-shell spherical head model registered to the Talairach human brain atlas. The solution space is restricted to Talairach cortical and hippocampal grey matter and includes 2394 voxels (7x7x7 mm resolution); each voxel containing an equivalent current dipole. The advantage of using the Talairach head model is that it allows precise neuroanatomical localization in standardized coordinates. The technical details of the LORETA method are extensively described in Pascual-Marqui et al. *(1994, 1999)*. In short, LORETA consists of voxel current density values (A/m^2) that is consistent with the EEG spectral power density at the scalp electrodes. The LORETA linear solution is characterized by the property that the activity at any given voxel must be as similar as possible to the average activity of its neighboring voxels. This property corresponds to the mathematical implementation of highly synchronized activity among neighboring neuronal populations.

The LORETA method has been previously validated through correct localization of epileptic foci, primary sensory, language and face processing areas (see Figure 4.3-6) *(Pascual-Marqui et al., 2002)*. Study 2 of this thesis is primarily based on LORETA. In addition to assessing training-related changes, a secondary aim of this study was the further validation of LORETA in the motor domain.

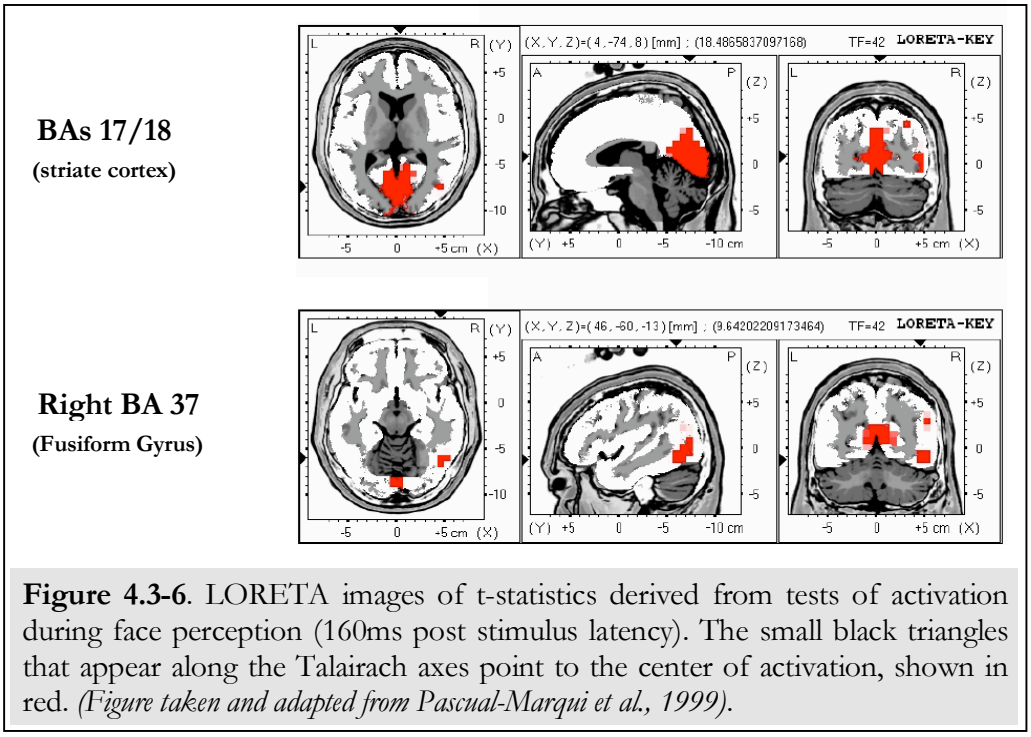


Figure 4.3-6. LORETA images of t-statistics derived from tests of activation during face perception (160ms post stimulus latency). The small black triangles that appear along the Talairach axes point to the center of activation, shown in red. *(Figure taken and adapted from Pascual-Marqui et al., 1999).*

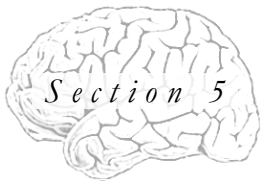
4.3.8 Advantages & disadvantages of EEG

As each neurophysiological method, EEG has many advantages that make it a very strong tool to explore brain activity. First of all, it provides a very high time resolution down to sub-millisecond resolution. Brain functioning is based on electric activity and EEG is the only method, applicable to humans, to directly measure electric neuronal activity. In addition, EEG – compared to PET or fMRI – is a comparatively cheap technique which easily allows to obtain data from large subject populations in order to enhance reliability of the data.

But EEG has several limitations, too. Scalp electrodes are not sensitive enough to detect individual action potentials, the electric unit of signaling in the brain or to identify whether the resulting electrical activity is releasing inhibitory, excitatory or modulatory neurotransmitters. Instead, the EEG picks up synchronized activity of a large number of neurons, which produces a greater voltage than the firing of an individual neuron. Secondly, EEG has a limited spatial resolution compared with other functional brain imaging techniques such as e.g. fMRI.

4.4 Summary

In the wide field of neuroscience various techniques are commonly used to investigate the structure and function of the brain. Each of these methods is associated with particular advantages and disadvantages and assesses different aspects and levels of information processing. Current studies aim for the combination of different methods to efficiently exploit their advantages to maximize information gain. Furthermore, continuous technical advancements and interdisciplinary cooperation contribute to an improved understanding of how the brain is built and how it works.



Section 5

MOTIVATION, OPEN QUESTIONS & SIGNIFICANCE

Section 5 aims to derive open questions and controversial issues from the pertinent literature that will be addressed by the empirical part of this thesis. It therefore highlights its general motivation and significance. General aims that apply for all three studies will be outlined in the beginning of this section followed by specific questions the individual experiments sought to answer.

5.1 General Motivation

The overall aim of the present thesis was to explore functional reorganization in the primary motor cortex as a result of longer-lasting training of elementary finger movements. This was largely motivated by the need to develop a better understanding of changes in functional activation linked with elementary motor practice. Reviewing pertinent literature on motor learning (see ▸Sections 1 & 3) yields much evidence for tremendous reorganization effects due to complex motor skill acquisition. Intricate patterns of reductions and increases of movement-related activation with respect to both, intensity and extent, but also shifts of activation within the motor network have been reported. Neural changes associated with the adaptation/modification of basic movement parameters in the context of motor learning have received little attention in the past. Hence, underlying mechanisms remain largely unclear. Given the differences in the neural control of complex vs. simple movements, as reflected (a) by different levels of activation strength and spatial extent and (b) by the recruitment of additional premotor and non-motor regions, it is conceivable that the pattern of training-induced changes is much more multifaceted in case of complex motor skills and certainly involves a variety of regions primarily associated with cognitive demands of complex movements. Putative interactions within strongly connected task-related neural networks limit the interpretation of changes occurring in single regions.

→ All experiments of this thesis were therefore explicitly designed to explore changes that accompany the practice of most elementary repetitive finger movements. Thereby the neural network of areas influencing the pattern of functional reorganization in M1 was intentionally held small.

The focus of this thesis is placed on changes specifically occurring in the primary motor cortex. M1 has previously shown to play a key role in controlling subjects' maximum tapping speed. Evidence has been provided by early single cell recording studies but also by recent neuroimaging work (see ▸Section 3.1 for a review of corresponding studies). The motor training used in all three experiments consisted of fast repetitive thumb tapping movements. The explicit aim was to increase maximum tapping speed. Thus, task and training characteristics point to a strong involvement of M1. Furthermore, as elaborated in ▸Section 3, the tremendous capability of M1 for functional reorganization has been consistently demonstrated in studies of motor learning and consolidation.

→ All experiments of this thesis assessed training-related changes in M1 for above-mentioned reasons. On the basis of the assumption that maximum-speed movements drive the motor cortex to operate at a maximum activation level, this thesis specifically seeks to address changes in M1 functioning that enable the control of training-induced increase in maximum tapping speed.

A third issue relates to the time-pattern of training-induced changes. The majority of previous studies have used rather short training durations (< 1h, exercised during one single training session). Another approach to explore training-related changes in functional motor control is represented by studies using professional musicians or athletes as subjects. This particular population has received intense and long-lasting (lifelong) training on specific movements and therefore serves as an adequate model of neuroplasticity (see ▸Section 1.4.1). However, medium training durations (in the range of days to weeks) have rarely been used in previous literature, thus leaving many interesting questions to be addressed.

→ Medium training durations (2 to 4 weeks of training on a daily basis) were used in all experiments reported in this thesis, thus expanding the short time window that has been extensively studied in the past.

Furthermore the thesis tries to contribute to the understanding of the relation between changes on the neural and on the behavioral level. It has been emphasized in ▸Section 1 that the challenge of future research is to address the relation between neural activity and behavior, given that this is necessary for the efficient use of basic research findings in the clinical context.

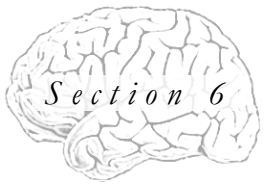
5.2 Specific Aims

Study 1 addresses the issue of training-related changes in M1 by assessing corticospinal excitability using TMS before and after a longer-lasting training that aimed at increasing maximum tapping speed of either the left or the right thumb. In addition, this study aimed to improve our understanding of the role of the ipsilateral hemisphere during motor training of the subdominant hand (▸Section 6).

Study 2 also investigated neural changes in M1 accompanying the extensive training of maximum-speed thumb tapping movements. However, in contrast to study 1, neural activity was assessed directly while subjects performed the trained movement. Neural activity, as recorded with EEG, was indicated by the extent of alpha-band desynchronization during movement performance compared to a non-movement baseline (▸Section 7).

In **Study 3** high-resolution fMRI was employed to reinvestigate the functional organization of finger representations in the hand region of the primary motor cortex. Besides addressing the question of somatotopic arrangement, this study primarily explored whether the arrangement of finger representations is changed by a longer-lasting elementary motor training of a single finger (▸Section 8).

Going one step further, the anticipated contribution of the above-mentioned three experiments to a deeper understanding of plasticity effects in the primary motor cortex over an extended time range may bring relevant clinical implications about. The data may be particularly relevant in the context of rehabilitation. Re-training programs were employed in diverse patient groups, however, the behavioral outcome has been inconsistent and the mechanisms and principles underlying potential training-related changes are not sufficiently understood. Thus, this thesis in part also aims to provide findings that can be applied to rehabilitative approaches, e.g. to develop more specific and efficient goals for motor training programs. In particular, this can be instrumental in supervising post-stroke training and in contributing to explanations of focal dystonia and its therapy. These significant issues will be taken up again in ▸Section 9.



EXPERIMENT / STUDY 1

Extensive Training of Elementary Finger Tapping Movements Changes the Pattern of Motor Cortex Excitability

Acknowledgements: This work was supported by an NCCR-grant to L.J. (Swiss National Foundation, Neural plasticity and repair).

6.1 Abstract

There is evidence of a strong capacity for functional and structural reorganization in the human motor system. However, past research has focused mainly on complex movement sequences over rather short training durations. In this study we investigated changes in corticospinal excitability associated with longer training of elementary, maximum-speed tapping movements. All participating subjects were consistent right-handers and were trained using either the right (experiment 1) or the left thumb (experiment 2). Transcranial Magnetic Stimulation (TMS) was applied to obtain motor evoked potentials (MEPs) from the abductor pollicis brevis (APB) muscle of the right and the left hand before and after training. As a result of training, a significant increase was observed in tapping speed accompanied by increased MEPs, recorded from the trained APB muscle, following contralateral M1 stimulation. In the case of subdominant hand training we additionally demonstrate increased MEP amplitudes evoked at the right APB (untrained hand) in the first training week. Enhanced corticospinal excitability associated with practice of elementary movements may constitute a necessary precursor for inducing plastic changes within the motor system. The involvement of the ipsilateral left M1 likely reflects the predominant role of the left M1 in the general control (modification) of simple motor parameters in right-handed subjects.

6.2 Introduction

Reorganizational changes in the central nervous system are thought to support learning processes. Use-dependent plasticity within the primary motor cortex (M1) through practice of voluntary movements is one such example. *(Karni et al., 1995; Hazeltine et al., 1997; Amunts K. et al., 1997; Classen et al., 1998; Muellbacher et al., 2001)*. Movement repetition, as one aspect of motor practice, has been intensively investigated in earlier studies where the focus was on complex (mostly sequential) movements. Training durations varied greatly, ranging from minutes to weeks. The within-session effects of movement repetition in previous studies do not provide consistent results for the accompanying neural activation, showing either decreases *(Karni et al., 1995; Karni et al., 1998) or increases (Grafton et al., 1992b; Iacoboni et al., 1996; Shadmehr & Holcomb, 1997)*. In contrast, consistency has been reported in the slowly developing increase of activation (several days up to weeks) *(Karni et al., 1995; Ungerleider et al., 2002; Hlustik et al., 2004)*. TMS-based studies have addressed the issue of motor training and results suggest expansion and increased excitability of the neural representation of specific muscles involved in the training task *(Cohen et al., 1993; Pascual-Leone et al., 1994; Classen et al., 1998; Cohen et al., 1998; Classen et al., 1999; Pascual-Leone A. et al., 2005)*. In addition to the application of diverse training paradigms in studies using untrained subjects, the investigation of skilled subjects has received much attention, professional musicians being of chief interest *(Munte et al., 2002)* because they represent an adequate model of neuroplasticity. Skilled compared to non-skilled subjects show reduced neural activation in primary and secondary motor areas when performing the same motor action *(Jäncke et al., 2000c; Lotze et al., 2003b; Haslinger et al., 2004; Koeneke et al., 2004)* – an effect that has been explained as reflecting the diminished neural effort required for a particular motor performance with a history of life-long, intense motor training.

Considerably less data are available on motor learning of more elementary movements, such as finger flexion/extension. Those movements belong to the motor repertoire all but since birth; they are frequently performed throughout life and form the basis of more complex, purposeful motor acts. While many

studies have examined changes in neural activation accompanying the stereotyped repetition of elementary movements *(Yetkin et al., 1996; Rajah et al., 1998; Dejardin et al., 1998; Carey et al., 2000b; Loubinoux et al., 2001; Tracy et al., 2001; Morgen et al., 2004)*, only very few have explicitly investigated effects of training in terms of modifying single movement parameters like direction, acceleration or speed. Classen and co-workers (1998) have elegantly shown that the stereotyped repetition of a simple finger movement results in strong plasticity effects within M1. Their results clearly suggest the establishment of a memory trace with which kinematic details of the practiced movement are encoded *(Classen et al., 1998; Classen et al., 1999)*. Training durations in studies on exercising elementary movements are generally in the range of several minutes. Thus, there is some need to study the neural activation changes associated with longer lasting motor trainings.

A further interesting question is whether the contra- and ipsilateral motor cortices are similarly or differently involved in the process of motor learning – especially in the case of subdominant hand training. Previous studies have uncovered several factors (e.g. hand dominance, task difficulty, and effort) which determine the involvement of the ipsilateral hemisphere in the neural control of unimanual movements *(Kim et al., 1993; Kawashima et al., 1993; Chen et al., 1997a; Chen et al., 1997b; Baraldi et al., 1999; Caramia et al., 2000; Kobayashi et al., 2003; Verstynen et al., 2005)*. There have however been very few investigations of asymmetrical hemispheric involvement in motor learning to date. Some studies suggest that the dominant motor cortex is involved in learning with the right **and** left hand, while the subdominant motor cortex is only active during learning with the subdominant hand, asymmetrical transfer of information via the corpus callosum being the result *(Halsband, 1992; Schulze et al., 2002)*.

To address the issue of elementary finger movements and training-related changes in M1, we assessed corticospinal excitability using TMS before and after training aimed at increasing maximum thumb tapping speed. Since previous studies have shown that sequential movements rely on activations in a distributed neural network *(Sadato et al., 1996a; Catalan et al., 1998; Harrington et al., 2000; Jäncke et al., 2000b; Haslinger et al., 2002)*, we decided to use simple finger

tapping training to avoid confounding influences from the entire motor system onto M1/S1. In addition, the present study aimed to improve our understanding of the role of the ipsilateral hemisphere during motor training of the subdominant hand.

6.3 Materials and methods

The current study consists of two experiments, both of which were designed to determine corticospinal excitability before and after motor training of elementary, repetitive thumb movements. Experiment 2 focused on motor training involving the right thumb (dominant hand) while experiment 2 investigated effects occurring during left thumb training (subdominant hand). Data for both experiments were acquired over a period of about 2 years. Due to technical constraints we used a different stimulation device in experiment 2 (see below). In addition to this, we introduced two further measurement time points in experiment 2 to delineate the learning-related time course more precisely. However, since the electrophysiological data resulting from the two experiments were not directly compared, it is unlikely that the methodological differences put any substantial limitations on the interpretation of the data.

6.3.1 Subjects

17 subjects took part in the two experiments (experiment 1: 10 subjects / 9 women, mean age 28.0 ± 2.9 years; experiment 2: 7 subjects / 4 women, mean age 27.7 ± 1.1 years). Handedness was assessed with the Annett Handedness Questionnaire (AHQ) *(Annett, 1970)* and the Hand Dominance Test (HDT) *(Steingruber, 1971; Jäncke, 1996)*. According to these tests, all subjects were classified as consistent right-handed subjects (CRH). None of the subjects showed signs of neurological or psychiatric disorders according to standard medical interviews. The study was approved by the local ethics committee. Each individual gave written informed consent. Tasks and testing procedures were in accordance with institutional guidelines and the study conforms to the Declaration of Helsinki (the code of ethics of the world medical association).

6.3.2 Transcranial magnetic stimulation

Magnetic Stimulation was delivered with commercially available stimulators with biphasic waveforms (experiment 1: *MagLite-r25 with TwinTop Option, Dantec Medical, Skovelunde, Denmark* / experiment 2: *Magstim 220, Whitland, Dyfed, UK*)

through figure of eight-shaped coils (experiment 1: *MCB70/* experiment 2: *Magstim Double 70mm Coil*) that were placed tangentially to the scalp, with the handle pointing backward and rotated away from the midline by 45°. This ensures that the first quarter-cycle of the cosine waveform of the current induced in the brain is directed in a posterior-to-anterior direction, while the biologically more effective following half-cycle is directed in the opposite direction.

The TMS procedure for every muscle recorded at any time point of measurement was strictly uniform. First, focal TMS was applied to the contralateral hand area of the motor cortex in order to determine the optimal scalp position for consistently eliciting motor evoked potentials of maximal amplitude in the target muscle. This position was marked on the scalp with a pen to ensure an identical coil placement throughout the experiment.

The resting motor threshold (RMT) was then determined to the nearest 1% of maximum stimulator output in the resting target muscle while maintaining the coil at the optimal position. RMT was defined as the minimal stimulus intensity sufficient to elicit MEP greater than 50μV base-to-peak amplitude in at least five out of ten trials *(Rossini et al., 1994)*. Stimuli were delivered no more frequently than one every 10 seconds. The intensity of TMS pulses during the experimental sessions was adjusted to 120% of the RMT in experiment 1 and 110% of the RMT in experiment 2. A total of 20 MEPs per muscle were recorded to ensure collection of enough data to compensate for high variability, a known problem in recording cortically induced MEPs *(Hess et al., 1987; Kiers et al., 1993)*.

6.3.3 Peripheral nerve stimulation

In order to control for changes of nerve and muscle excitability, maximal compound muscle action potentials (CMAPs) were determined by supramaximal electrical stimulation of the median nerve at the wrist for the left and right abductor pollicis brevis (APB) muscle, using a conventional electrical stimulator (*SIGMA Medizin-Technik GmbH, Germany*). Since we did not detect a significant change of the CMAP amplitude as a consequence of training in experiment 1, peripheral stimulation was no longer carried out in experiment 2.

6.3.4 Electromyography (EMG) recordings

Motor evoked potentials (MEPs) were recorded from the right and left APB using gold cup surface electrodes (11 mm diameter) filled with contact gel in a belly tendon montage. In experiment 1 MEPs from the right abductor digiti minimi (ADM) were additionally recorded in 7 of 10 subjects to test for the specificity of the training effect, since the ADM was not explicitly involved in training. To avoid high impedances, the skin was carefully prepared with cleaning pads soaked in alcohol and abrasive gel. The EMG signal was recorded with a conventional EMG electromyograph (*SIGMA Medizin-Technik GmbH, Germany*) using a bandpass of 20 Hz - 3 kHz. The signal was digitized at a frequency of 50 kHz and stored on a personal computer for off-line analysis. Pulses were only applied in epochs without apparent baseline EMG activity.

6.3.5 Motor training

The motor training consisted of elementary, repetitive tapping movements performed with the right or left thumb (tapping on a key), strongly involving the APB muscle. In contrast to previous studies, we used training durations of several weeks (experiment 1: four weeks / experiment 2: two weeks of daily training; *for explanation, see below*). The subjects were given the aim of increasing maximum tapping speed. After the pre-training TMS session subjects were precisely instructed in how to carry out the motor training. They were told to put the right hand beneath the computer keyboard, with the thumb positioned on the *ENTER* key of the numeric keypad (*CTRL* key for training with the subdominant left thumb) and the remaining digits resting aside. Subjects were further advised to only involve the thumb during the tapping periods and to prevent the other digits from moving. One daily training session consisted of 30 consecutive trials that were made up of a movement execution period (20 sec) and a resting period (40 sec). The tapping training was carried out by the subjects on their home computers. In house software (*TapTrainer*) was used to guide the daily training sessions and to record particular training parameters, for example, Inter-Tap-Intervals (ITIs) as indicators for tapping speed. This gave us the opportunity to track the course of training. We were therefore able to en-

sure that subjects accomplished the training regularly and in accordance with the instructions.

6.3.6 Experimental protocol

Experiment 1. Corticospinal as well as peripheral nerve excitability was determined before training (Exp1-T1) and after completion of the 4 weeks of training (Exp1-T2). For this, subjects were seated in a comfortable chair with forearms supported on a cushion and were instructed to keep their hands relaxed during the measurements. At the beginning of each measurement CMAPs were determined for the left and right APB. Afterwards MEPs were elicited from the target muscles (left and right APB, right ADM) in pseudo-randomized order. The motor training was carried out only with the right thumb (=dominant hand) and on a daily basis for an overall duration of *4 weeks* (one day without training per week – resulting in a total of 24 training sessions).

Experiment 2. The experimental setup was the same as in experiment 1, with the exception that the left thumb now underwent motor training (=subdominant hand). In experiment 1, most pronounced increases in tapping speed were observed during the first training days. For experiment 2, we therefore decided to shorten the overall training duration to *2 weeks* (with one day without training per week – resulting in a total of 12 training sessions) and to focus on the period of training where behavior changes are greatest. In order to track modulations of corticospinal excitability in the left and right hemisphere in more detail, we recorded MEPs from the left and right APB at four time points: before training had started (Exp2-T1), 30 minutes after the first training session (Exp2-T2; both measurement and the first training took place in our laboratory), after 6 training sessions, that is, one training week (Exp2-T3), and after 12 training sessions, when training was fully completed (Exp2-T4). Based on the results of our first experiment, we abstained from peripheral stimulation and from additionally recording MEPs from the ADM muscle.

6.3.7 Statistical analysis

Data were analyzed using standard parametric statistics. Given that all TMS and CMAP measurements were registered during complete muscular rest, we controlled whether or not subjects did profit from training and gained speed by analyzing behavioral data recorded by the TapTrainer software (Inter-Tap-Intervals: ITIs). For this purpose we calculated a mean ITI for each training session and further analyzed these mean values using a repeated measures ANOVA with session number as within-subject factor. Due to recording problems of the TapTrainer software in two subjects in the second half of experiment 1, the ANOVA was calculated with 12 factor levels (= number of sessions) for both experiments. In experiment 1, only data of the first 12 training sessions were used. Increases of maximum tapping speed across the training were tested using trend analyses supported by SPSS software. Since statistics for multivariate tests cannot be calculated when there are more factor levels than subjects, Greenhouse-Geisser corrections for degrees of freedom were used to correct for possible violations of homoscedasticity *(Keselman et al., 2001)*. In order to evaluate the training effect in experiment 1 over the whole training duration of 4 weeks, we determined mean ITIs for the beginning and for the end of training by averaging the recorded ITIs for the first three and for the last three training sessions for each individual separately. Additionally, changes in ITI variability were assessed by determining the averaged standard deviation of ITIs for the beginning and for the end of training. Mean ITIs and ITI variability for the two time points were compared using paired t-tests. To compare the magnitude of training effect between the two experiments we conducted a repeated measures ANOVA with 'time' (pre- vs. posttraining) as within-subject factor and 'study' (right-thumb vs. left-thumb training) as between-subject factor (involving the first 12 training sessions for both experiments).

MEP amplitudes for each target muscle and time point of measurement were determined (by averaging peak-to-base amplitudes over 20 single trials) and subjected to a two-way repeated measures ANOVA with *time point of acquisition* (experiment 1: T1, T2 / experiment 2: T1 – T4) and *stimulated hemisphere* (left vs. right M1) as within-subject factors. Wilks Lambda was computed in the context

of multivariate testing to conform to possible problems in homoscedasticity *(O'Brien & Kaiser, 1985)*. Post hoc analyses were carried out using Bonferroni-corrected t-tests for paired samples, applying the correction procedure by Holm *(Holm, 1979)*.

Since p-values strongly depend on sample size we additionally calculated effect size measures to obtain information on how strong an effect is. ETA^2 (η^2) is reported in multivariate ANOVA statistics and describes the variance attributed to the independent variable of interest. For the t-Tests, Cohen's d *(Cohen, 1988)* was determined $[d = M_1 - M_2 / \sigma_{pooled}]$, that is, the difference between two means divided by the pooled standard deviation. The pooled standard deviation is the square root of the average of the squared standard deviations *(Rosnow & Rosenthal, 1996)*. According to Cohen an effect size of $d > 0.5$ is considered as being moderate, while $d > 0.8$ is considered as being large *(Cohen, 1988)*.

6.4 Results

All subjects tolerated the single TMS pulses very well. Thus, there was no sign of discomfort and negative emotions, which might have influenced the results.

6.4.1 Experiment 1

One of the subjects was excluded from data analysis because of an injury sustained to the left wrist less than a year before study commencement. The injury might have altered corticospinal excitability and plasticity (Facchini et al., 2002; Zanette et al., 2004).

Behavioral Results. Due to recording problems of the TapTrainer software in two subjects, the calculation of a repeated-measure ANOVA for all subjects and training sessions was not possible. Instead, we determined mean ITIs for the beginning and for the end of training by averaging the recorded ITIs for the first three as well as for the last three training sessions for each individual separately. These mean ITIs underwent a paired t-test for 9 subjects that revealed a significant decrease of the ITIs [$T(8) = 2.591$, $p = 0.032$, *one-tailed*]. More detailed exploration of the data unveiled a marked increase of tapping speed at the end of training in only 7 of the 9 subjects. Since the focus of this study was to investigate changes of cortical plasticity resulting from behavioral training and because we were not sure about the reasons for this negative finding, we decided to exclude the 2 subjects who obviously did not profit from the training. Thus, as depicted in figure 1c, calculating the paired t-test for the remaining sample of 7 subjects resulted in an even more significant effect of training [$T(6) = 3.41$, $p < 0.01$, *one-tailed*, $d = 1.57$]. ITI variability did not change from pre- to posttraining measurements.

We additionally carried out a repeated-measures ANOVA for 7 subjects (showing a training effect) and the first 12 training sessions to make comparisons with the left-thumb training. The results of this ANOVA show a highly significant

training effect [*F(3.3,19.5) = 5.517, p = 0.006,* η^2 *= 0.48*]. Subsequently conducted trend analyses revealed a linear trend [*F(1,6) = 8.38, p = 0.028,* η^2 *= 0.58*], a quadratic trend [*F(1,6) = 10.34, p = 0.018,* η^2 *= 0.63*] and a cubic trend [*F(1,6) = 10.7, p = 0.017,* η^2 *= 0.64*]. As can be seen in figure 1a, these trends are qualified by a strong decrease in ITIs during the first four training sessions followed by a period of less pronounced performance gains. The description of further results of cortical and peripheral stimulation includes only the 7 subjects showing a training effect in terms of faster tapping.

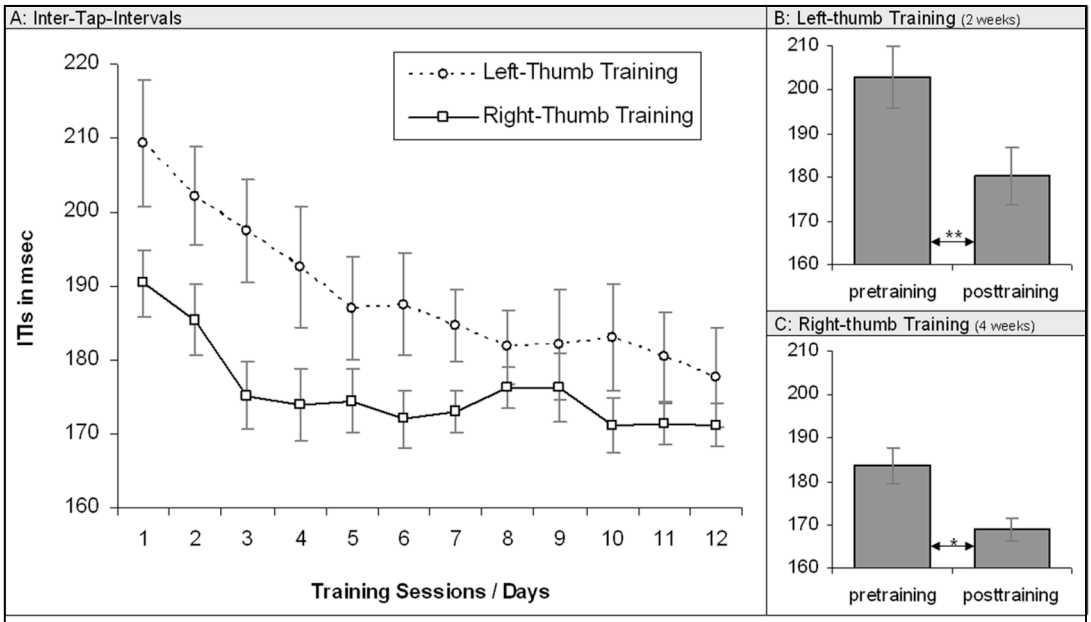


Figure 6.4-1: Inter-Tap-Intervals (ITIs) in msec. Left panel (A): Decrease of ITIs throughout the first 2 weeks of training for the left-thumb (dashed line) and for the right-thumb (solid line) training group. Right Panel: Averaged ITIs for the first three training sessions (= pretraining) and for the last three training sessions (= posttraining) separately for the left-thumb training group (B) and for the right-thumb training group considering the whole training duration of 4 weeks (C). Error information is given as S.E.

CMAPs. In order to control for changes of nerve and muscle excitability, maximal compound muscle action potentials (CMAPs) were determined by supramaximal electrical stimulation of the median nerve at the wrist for the left and right APB. Comparing pre- and posttraining measurements by means of a t-test for paired samples, we did not observe a significant difference [*mean CMAPs for the right APB: 6.87 ± 2.1 mV at T1 vs. 7.64 ± 3.2 mV at T2 / for the left APB: 6.36 ± 1.79 mV at T1 vs. 6.60 ± 1.5 mV at T2*].

Resting Motor Threshold. Mean RMT was *33.3% [SD: 5.7]* of maximum stimulator output for the right APB, *32.9% [SD: 6.3]* for the left APB and *27.6% [SD: 5.2]* for the right ADM. The RMT did not change as a result of training [*paired t-tests for all muscles: $p > 0.1$*].

Motor Evoked Potentials. The two-way repeated-measures ANOVA (factor1: right APB vs. left APB; factor2: Exp1-T1 vs. Exp1-T2) revealed a significant interaction between the two factors [$F(1,6) = 8.56$, $p = 0.026$, $\eta^2 = 0.59$]. Subsequent post hoc t-tests for paired samples showed that this interaction effect was qualified by a significant increase of the MEP amplitudes recorded from the right APB at post- compared to pretraining measures [$T(6)=-2.31$, $p=0.060$, *two-tailed*, $d = 0.98$] (see figure 2). An increase of MEP amplitudes was not apparent for the left untrained APB muscle. Furthermore, MEP amplitudes evoked in the right ADM, which was not involved in training and, thus served as another control, did not change during the course of training [$p > 0.1$].

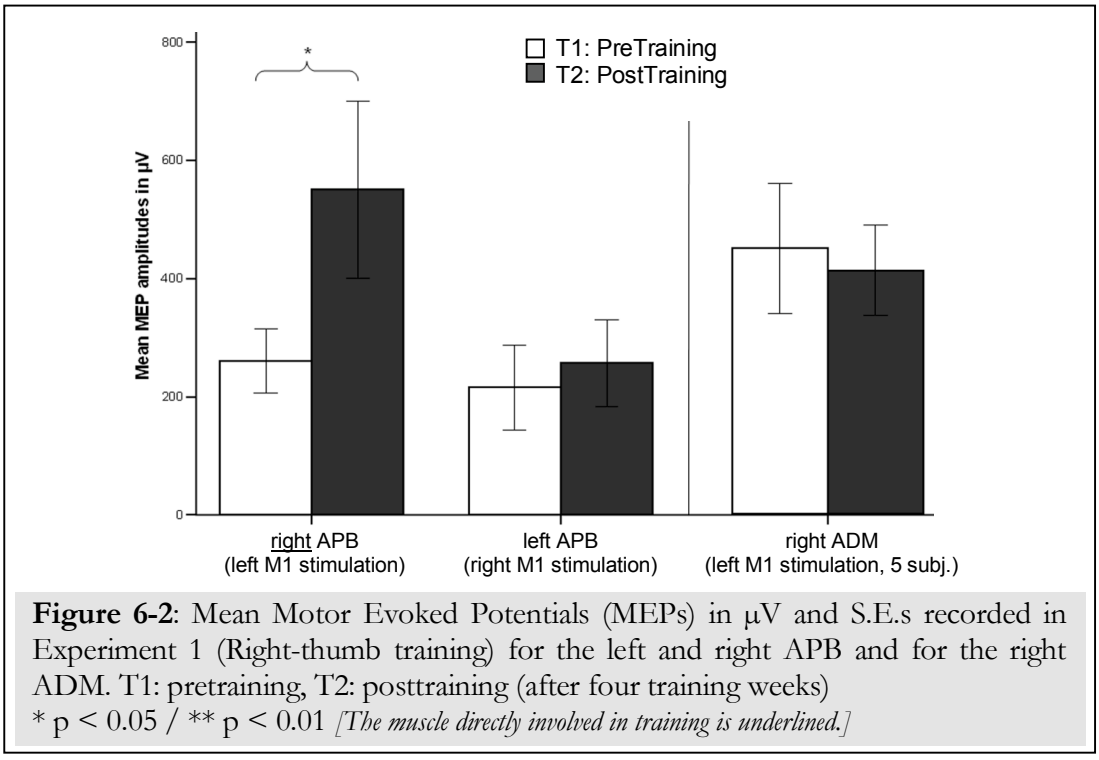


Figure 6-2: Mean Motor Evoked Potentials (MEPs) in µV and S.E.s recorded in Experiment 1 (Right-thumb training) for the left and right APB and for the right ADM. T1: pretraining, T2: posttraining (after four training weeks)
* $p < 0.05$ / ** $p < 0.01$ *[The muscle directly involved in training is underlined.]*

As suggested by previous studies *(Rossini et al., 1994; Ziemann et al., 1998b)*, we additionally calculated the relation of absolute MEP amplitude values to periph-

erally recorded CMAPs. Subjecting the *relative MEPs* to the same ANOVA model with *muscle* and *time* as within-subject factors resulted in a comparable interaction effect accompanied by a significant post-hoc t-test *[T1<T2 (right APB): T(6)=-2.77, p=0.034, two-tailed, d = 1.27]*.

6.4.2 Experiment 2

Behavioral Results. Analyzing the mean ITIs obtained for each training session in the repeated measures ANOVA with 12 factor levels (= 12 training days) revealed a highly significant training effect [$F(3.6,22.5) = 20.8$, $p < 0.001$, $\eta^2 = 0.77$]. Subsequently conducted trend analyses revealed a strong linear trend [$F(1,6) = 76.0$, $p < 0.001$, $\eta^2 = 0.93$] and a significant quadratic trend [$F(1,6) = 26.3$, $p = 0.002$, $\eta^2 = 0.81$]. These trends are qualified by strongly decreasing ITIs during the course of training. As can be seen from figure 1a, the ITI decrease is steeper for the first five days, thus causing the quadratic trend. Comparison of the mean ITIs of the first and last three training sessions reveals a significant decrease of the ITIs after two weeks of training [$T(6) = 11.526$, $p < 0.01$, *two-tailed*, $d = 1.12$] (see figure 1b). ITI variability decreased from pre- to posttraining measurements [$T(6) = 2.017$, $p = 0.045$, *one-tailed*]. Comparing the magnitude of training effect between experiment 1 and 2 (considering the first 12 training sessions of both studies) revealed a significant study x time interaction [$F(1, 12) = 6.51$, $p = 0.025$, $\eta^2 = 0.35$] qualified by a significantly stronger training effect for the left compared to the right-thumb training.

Resting Motor Threshold. Mean RMT was 49.86% *[SD: 1.86]* of maximum stimulator output for the right APB and *53.86% [SD: 7.11]* for the left APB. The RMT did not change as a result of training [*paired t-tests for all muscles: $p > 0.1$*].

Motor Evoked Potentials. The two-way repeated-measures ANOVA (factor1: right APB vs. left APB; factor2: Exp2-T1 pretraining, Exp2-T2, Exp2-T3, Exp-T4 posttraining) revealed a significant interaction between the two factors [$F(3,4) = 6.54$, $p = 0.05$, $\eta^2 = 0.83$]. Mean MEP amplitudes for the left and right APB are displayed in figure 3. Inspection of the figure revealed a linear trend

(increasing MEPs during the course of training) for the left APB. Formal testing by trend analysis revealed a significant positive linear trend [*F(1,6) = 9.58, p = 0.02,* η^2 *= 0.62*]. For the right APB (which was not explicitly trained) there was no significant linear trend but a tendency toward a quadratic trend [*F(1,6) = 3.2, p = 0.12,* η^2 *= 0.35*]. Closer examination of the data showed increased right-sided APB MEPs at Exp2-T2 and Exp2-T3 [*T1<T2: T(6) = -1.50, p = 0.18, two-tailed, d = 0.63 / T1<T3: T(6) = -1.99, p < 0.94, two-tailed, d = 0.95*]. While the left M1 seems to be involved at the beginning of training, the right M1 shows a significant enhancement of MEP amplitudes only at Exp2-T3 and Exp2-T4, not immediately after the first training session [*T1 < T3: (T(6) = -3.68, p = 0.01, two-tailed, d = 1.60 / T1 < T4: T(6) = -3.68, p = 0.008, two-tailed, d = 1.52*].

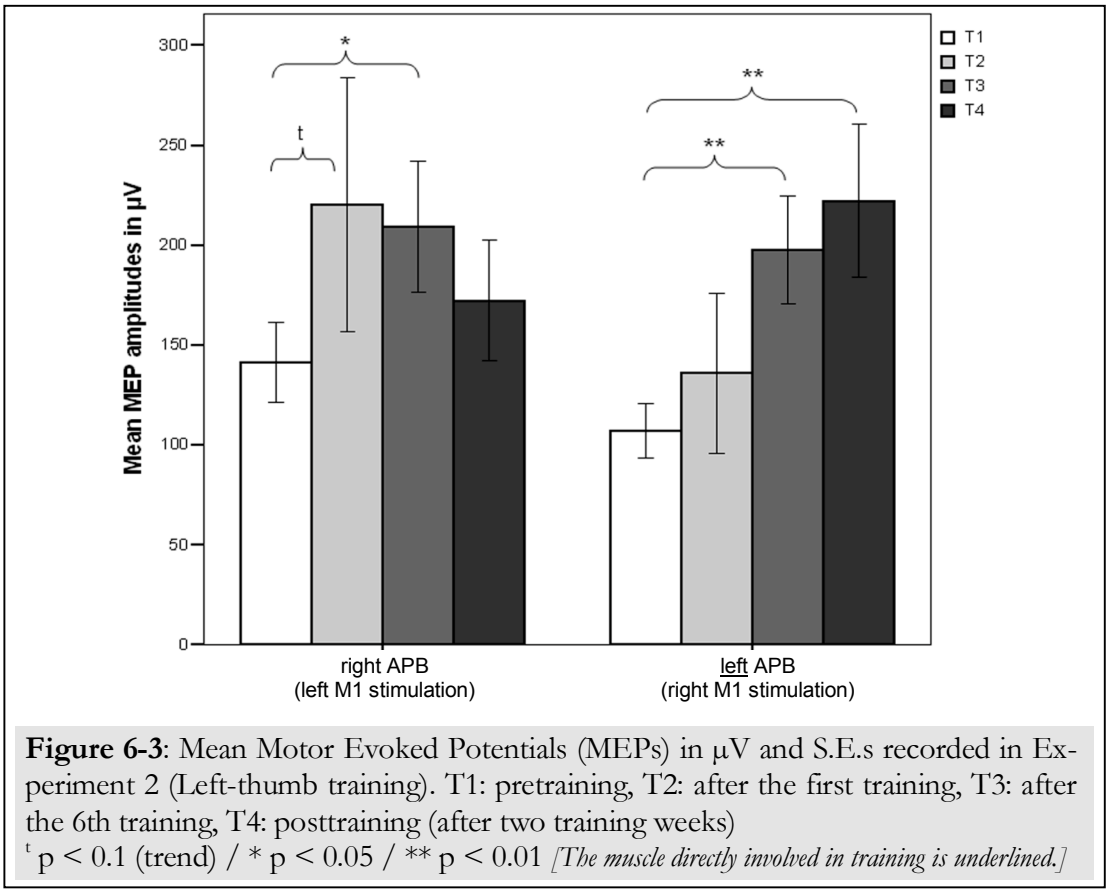


Figure 6-3: Mean Motor Evoked Potentials (MEPs) in µV and S.E.s recorded in Experiment 2 (Left-thumb training). T1: pretraining, T2: after the first training, T3: after the 6th training, T4: posttraining (after two training weeks)
^{t} p < 0.1 (trend) / * p < 0.05 / ** p < 0.01 *[The muscle directly involved in training is underlined.]*

6.5 Discussion

The current set of experiments was designed to investigate changes in motor cortex excitability with concomitant intense, longer-lasting training of thumb tapping speed. Common to both experiments was the main finding of a pre- versus post-training increase in the mean MEP amplitude as recorded at the trained APB muscle, a result that indicates an increase in corticospinal excitability. Our data further indicate a differential involvement of the two hemispheres during subdominant-hand training, with the ipsilateral left M1 (dominant) playing a considerably greater role, particularly during the first training week.

6.5.1 Hand dominance determines the magnitude of speed increase

Comparisons of training effect size between the two experiments revealed a significant between-group difference ($p = .025$) qualified by larger speed gains in the left-thumb training group. These subjects were able to tap with the left thumb at the end of the 2-week training as fast as the right-thumb training group could with the right thumb prior to training. Given that experiment 2 was exclusively designed to examine the first two weeks of practice, providing greater time resolution, statements about further speed gains cannot be made with certainty. Even though the strongest decline of ITIs occurs during the first five training sessions, the "learning curve" did not reach a stable plateau before conclusion of the 2 weeks of training, suggesting at least a small potential for further gain. Interestingly, only training of the left thumb resulted in a decrease of ITI variability over time. The decrease of mean ITIs may therefore partly result from a smaller proportion of occasionally produced long ITIs, which might have tampered the mean ITI before training. Our data are consistent with early behavioral studies proving hand asymmetry for mean ITIs and ITI variability *(Annett et al., 1974; Peters, 1976; Hammond et al., 1988)*. Moreover, Peters (1976) demonstrated a loss of asymmetry in tapping speed after prolonged practice of both hands. Generally, our behavioral data indicate the dominance of the right hand in all our subjects by revealing the greater effort required to gain speed in finger tapping when pretraining levels are already high. In contrast, more prominent changes can be induced at much shorter training intervals in the

subdominant left hand because it is less proficient in fine-motor skills. The specific increase of regularity in tapping movements might be one factor which contributes to the larger training gains for the left thumb compared to the right.

6.5.2 Training-related increase of corticospinal excitability

To our knowledge, the current study is one of the first to investigate long-term training of an elementary finger movement using TMS. The majority of other pertinent studies to date have employed motor skill learning of more or less complex movements (e.g. finger movement sequences) over rather short training durations *(Pascual-Leone et al., 1994; Karni et al., 1995; Hazeltine et al., 1997; Shadmehr & Holcomb, 1997; Classen et al., 1998; Cohen et al., 1998; Andres & Gerloff, 1999; Seidler et al., 2002; Nyberg et al., 2005; Pascual-Leone A. et al., 2005).*

Performance gains observed in the present study were accompanied by an increase of the mean amplitude of MEPs recorded from the trained muscle evoked by contralateral TMS. The amplitude of MEPs is an indicator of the level of excitability of the part of the corticospinal tract that controls the corresponding muscle and can therefore be used as a measure of motor training induced changes in corticospinal excitability. The increase in excitability is supposed to lead to a situation where the current spread from the stimulator gains access to more cortical units which contribute to increase the sum potential at the spinal neuron, thus resulting in a larger muscular response.

In interpreting the results, it is important to distinguish between synaptic changes within M1 (e.g. unmasking of previously silent synaptic connections; long-term potentiation or depression) and changes in the input to M1 from other structures – an aspect that is often neglected *(Donoghue et al., 1990; Jacobs & Donoghue, 1991; Hallett, 1995; Ridding & Rothwell, 1997)*. The current study design focused on changes within M1, making it impossible to determine whether alterations of synaptic functioning intrinsic to M1 or changes in the input to M1 increased the excitability of M1. We have however good reason to favor the former explanation. The tapping movement was performed at maximum speed with ITIs of ~200ms. Toma et al. provide electrophysiological data suggesting that the rhythm of movements rather than each individual move-

ment may be controlled at a movement rate of 3-4 Hz (Toma et al., 2002). This finding may support the idea of reduced involvement of motor regions typically associated with motor preparation and makes an increase in tonic input from these regions rather implausible. Further support is provided by studies showing robust correlations between movement velocity and the intensity of the discharge pattern of M1 neurons *(Humphrey, 1972; Ashe & Georgopoulos, 1994)*, indicating that the primary motor cortex is strongly involved in controlling the subjects' maximum tapping speed. Consistent with this is a recent study by Jäncke et al. (2004) demonstrating a decrease in maximum finger tapping speed following the disruption of M1 by low-frequency rTMS *(Jäncke et al., 2004)*. In view of the preceding, we interpret our data as reflecting the increased involvement of M1 neurons in meeting the explicit requirement of gaining speed through tapping training. However, external influences from basal ganglia or cerebellum to M1 cannot be excluded and this needs to be addressed in further studies.

It is theoretically possible for the observed modulations of MEP amplitudes to result from excitability changes at the level of either the spinal cord or the peripheral nerve. By assessing CMAPs via supramaximal electrical stimulation of the median nerve *(Rossini et al., 1994; Ziemann et al., 1998b)* we can rule out changes in peripheral nerve and muscle excitability. However, we cannot fully exclude changes at subcortical level, for example, brain stem or spinal cord. Nevertheless, we suggest the site where this form of plasticity takes place to be more likely of cortical than subcortical nature. Support for this hypothesis comes from a study by Muellbacher et al. (2001) showing that short-term practice of a repetitive ballistic pinch task led to a significant increase in MEP amplitude evoked by TMS, while MEP amplitudes evoked by direct stimulation of the corticospinal tract were not facilitated *(Muellbacher et al., 2001)*. It is likely that these findings can be applied at least to the early MEP changes of the present study (Exp2-T2).

Although neural changes accompanying long-term training of elementary movements (e.g. finger tapping) have not been addressed so far, we try to place our results in the context of previous work examining training effects of complex motor skill learning. Given that conventional neuroimaging fMRI- and

PET-based methods measure functional brain activation during the performance of movements and that TMS-based studies record amplitude of motor evoked potentials normally during complete muscular rest, a cross-method comparison of results is difficult. Neuroimaging studies on motor training will not therefore be considered here. To date there is one TMS study examining changes associated with longer motor training in healthy human subjects. In this study from Pascual-Leone et al. (1995), subjects practiced a finger movement sequence over the course of 5 days, this resulting in an enlargement of cortical motor areas that target those muscles involved in the practiced sequence. The motor training resulted also in a decreased activation threshold *(Pascual-Leone et al., 1995)*. An increase in M1 excitability at posttraining measures has been shown also and consistently in TMS studies using much shorter training periods (one training session lasting several minutes up to one hour) *(Muellbacher et al., 2001; Hayashi et al., 2002; Garry et al., 2004)*. Recent studies have been carried out to evaluate diverse motor trainings (mainly constraint-induced-therapy approaches) in stroke patients by means of TMS, and first results also suggest increased TMS motor map areas in the contralateral motor cortex following treatment, indicating increased excitability *(Classen et al., 1998; Park et al., 2004)*. We assume that the increased corticospinal excitability which accompanied motor training in the present study is a necessary prerequisite for inducing plastic changes within the motor cortex – a condition that is present beyond the actual motor performance.

6.5.3 Ipsilateral M1 involvement during left-thumb training

Experiment 2 of the present study was designed to analyse motor cortex excitability in more detail across four time points. Special interest was placed on the involvement of the ipsilateral hemisphere. The existing literature emphasizes factors like *hand dominance* and *task complexity/difficulty* as playing a role in determining the involvement of the ipsilateral hemisphere during unimanual movements *(Kim et al., 1993; Sadato et al., 1996a; Chen et al., 1997b; Kawashima et al., 1998; Baraldi et al., 1999; Cramer et al., 1999; Caramia et al., 2000; Alkadhi et al., 2002b; Kobayashi et al., 2003; Huang et al., 2004; Verstynen et al., 2005)*.

Our results show MEPs evoked from the left and right hemisphere M1 region to be differentially affected by the motor training throughout the course of 2 weeks. MEP amplitudes evoked from the contralateral right M1 were significantly enlarged at Exp2-T3 (*after 6 trainings*) and Exp2-T4 (*after 12 trainings*) but **not** directly after the first training session (Exp2-T2). Enhanced corticospinal excitability was also observed in case of left M1 stimulation; however, this effect was limited to the second and third time point of measurement (Exp2-T2, Exp2-T3). In line with previous studies *(Beltramello et al., 1998; Kobayashi et al., 2003)*, our data thus suggest ipsilateral M1 activation during simple movements performed with the subdominant hand. We think that *effort* – as a consequence of task difficulty - may play a crucial role in our case. Subdominant thumb tapping in maximum speed is certainly associated with high processing demands on the motor areas since the left hand, and more so the left thumb, are much less skilled compared to the right hand in consistent right-handers. A very recent study by Lutz et al. (2005) reported cortical *rate effects* of similar magnitude for the subdominant and dominant hand, while at the same time showing lower tapping rates for the subdominant hand. This result led them to suggest that the subdominant motor cortex might operate at suboptimal control levels, although maximum neurophysiological activation has been reached during the maximum tapping task. Our data further suggest that the left motor cortex is particularly involved during the first training week. It is tempting to bring this finding, once again, in association with the left-hemisphere dominance in right-handers. It was shown that the subdominant hand produces a stronger rate effect in the contralateral hemisphere than the dominant hand in paced finger tapping conditions *(Jäncke et al., 1998a)*. Thus, it was argued that the subdominant right motor cortex would have less processing capacities to control the subdominant hand during faster finger tapping rates *(Jäncke et al., 1998a; Jäncke et al., 1999)*. One could therefore speculate that the increase in excitability of the dominant left M1 reflects increased involvement at the beginning of training – at a time when the right-hemisphere motor system is not yet fully capable of controlling fast tapping movements. Based upon the results of their study, Agnew et al. (2004) hypothesize that "the right hemisphere system is less skilled at controlling variable rate movements", and suggest further "that the specialization of the left

hemisphere corticostriatal system for dexterity is reflected in asymmetric mechanism for movement rate control". We propose that the enhancement of MEPs after left M1 stimulation is triggered by the preceding exercise, and that this however represents a rather general increase of corticospinal excitation as a precondition for inducing more specific plastic changes at later stages of the parameter adaptation process.

We did not assess short-term changes of M1 excitability (e.g. after one training session) in the right-thumb training group. In order to provide an answer to the upcoming question whether the ipsilateral right M1 is involved in the beginning of right-thumb training, we refer to previous literature. It was repeatedly shown that the dominant M1 is involved in learning with the right and left hand while the subdominant motor cortex is exclusively active during learning with the subdominant hand, thus, providing evidence for an asymmetry of information transfer via the corpus callosum *(Halsband, 1992; Schulze et al., 2002)*. The TMS study by Pascual-Leone et al. (1995) investigating changes in M1 excitability following short-term motor training of the right hand also demonstrates a limitation of the facilitation effect to the left, trained M1 throughout the entire course of training *(Pascual-Leone et al., 1995)*. Even though the involvement of the right M1 during right-thumb training seems implausible, particularly in the case of elementary tapping movements, this issue needs to be explored further.

6.5.4 Time course of neural excitability during motor learning

Current literature suggests that motor skill learning, and motor consolidation, is accomplished in at least 2 distinct stages – (1) a fast learning, initial, within-session improvement phase and (2) a slow learning phase, consisting of delayed, incremental gains in performance during continuing practice. While neurophysiological data has yet to provide a clear substrate for the first learning stage, slow learning has been consistently associated with marked increases in M1 activation *(Ungerleider et al., 2002)*. After years of most intense motor skill training, musicians exhibit decreased activation when compared to unskilled subjects on comparable motor tasks, an effect that is commonly associated with diminished neural effort necessary to perform the movements. This is consistent with the

idea that more neuronal involvement is needed at the beginning of training in order to build up a larger network or to implement task-specific routines. This increase in processing capacities is the basis for shaping more efficient networks at later training stages. The hypothesis seems plausible that the time course of neural excitability associated with motor training of simple repetitive tapping movements resembles that of more complex motor skill learning on a much shorter time scale. Based on our training protocol, we would predict an increase in M1 excitability during the first training days, followed by a decrease of excitability by the end of training as performance places less demand on cortical control. The design of experiment 2 with 4 measurement time points enables us to partly scrutinize the proposed hypothesis. However, data for the right hemisphere (contralateral to the trained hand) indicate continuously increasing MEP amplitudes. There is no decline in excitability after 2 weeks of training. This might indicate that the hypothesized process of expanding processing capacities is not completed in this case. Considering that tapping speed did not reach a stable plateau after 2 weeks of training, we argue that in our case incomplete training experience may explain the lack of a decline in motor cortex excitability at the end of training. We observed a pattern of changes in the left motor cortex (ipsilateral to the trained hand) that may fit the hypothesis of an increase of excitability in the first training week followed by a decrease after another training week. However, as already discussed, we suggest that the decline in left M1 excitation at the end of training is more likely an effect resulting from the slowly developing increase in processing capacities of the contralateral right motor cortex, which is predominantly associated with left hand movements.

6.6 References

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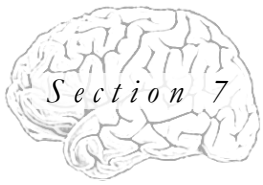

EXPERIMENT / STUDY 2

How finger tapping practice enhances efficiency of motor control.

Acknowledgements: This work was supported by an NCCR-grant to L.J. (Swiss National Foundation, Neural plasticity and repair).

7.1 Abstract

Maximum-speed movements have been suggested to put maximum neural control demands on the primary motor cortex (M1); hence we are asking how M1 function changes to enable enhanced maximum movement rates induced by longer-lasting practice. Cortical function was assessed by recording task-related spectral EEG alpha power. LORETA was used to localize intracortical neuronal sources. The main result is a decrease in neural activity in the left hemisphere (ipsilateral to trained hand) from pre- to posttraining whereas right hemispheric activity remained constant across training. This likely reflects the initially limited capacity of the right hemisphere to control demanding left-hand movements, but also highlights its ability to become more efficient with training, indicated by reduced involvement of the left M1 after training.

7.2 Introduction

An enormous amount of work has been carried out to study the underlying neural mechanisms of motor skill learning at various time scales *(Karni et al., 1995; Pascual-Leone et al., 1995; Classen et al., 1998; Muellbacher et al., 2001; for a review see Doyon & Benali, 2005; Nyberg et al., 2006)*. However, neural changes accompanying training-induced modifications of single movement parameters (for instance direction, acceleration or speed) have received comparatively little attention in previous experiments. In an elegant study, Classen et al. *(1998)* demonstrated that the stereotyped repetition of a simple finger movement results in strong changes of basic functional properties of the primary motor cortex (M1) as assessed with Transcranial Magnetic stimulation (TMS) *(Classen et al., 1998)*. The present study employed a motor training that explicitly aimed to increase movement rate. Therefore, we expected behavioral measures to be different before and after training. Consistent with the concept of the rate effect, one would expect that a higher movement rate demands for increased neural activation in M1. Several neuroimaging studies have consistently proven a rate effect for M1 but also for several non-primary motor areas (cerebellum, and partly premotor cortices) *(Schlaug et al., 1996; Jäncke et al., 1998a; Jäncke et al., 1998b)*. In addition, Toma et al. (2002) showed that task-related alpha and beta power changes, as measured with electroencephalography (EEG), are also sensitive to reveal a neural *rate effect (Toma et al., 2002)*. It has been proposed that the *rate effect* is due to increasing processing demands placed on the motor areas with increasing movement rates. It was further assumed that finger tapping at maximum speed requires the contralateral primary motor area to operate at a maximum activation level. A very recent study has provided evidence that the amount of neuronal effort (reflecting the control demands necessary to control the tapping movement) is the critical variable determining the activation within M1 and not the physical tapping speed *(Lutz et al., 2005)*. It was shown that maximum-speed tapping using either the left or right index finger caused similar amounts of contralateral M1 activity, although the maximum tapping rate was different for the two hands. While this finding highlights the influence of hand asymmetry (suggesting that the subdominant motor cortex operates at suboptimal control lev-

els), effects of experimentally induced, shorter-lasting motor trainings on the neural control of repetitive movements at maximum-speed have yet to be explored.

The present study therefore aims to assess neural changes in the sensorimotor cortex that accompany a four-week-lasting training of maximum-speed thumb tapping movements. Task-related changes of spectral alpha band power, as computed from the EEG signal and intracortically localized using LORETA (Low Resolution Brain Electromagnetic Tomography), served as an indicator for neural activation of the motor cortex and were therefore used to quantify training-related changes.

7.3 Materials & Methods

7.3.1 Subjects

8 healthy subjects took part in the study (6 women, mean age 25.0 ± 3.0). All subjects were consistent right-handers (Annett Handedness Questionnaire *(Annett, 1970),* Hand Dominance Test *(Steingruber, 1971; Jäncke, 1996)*). The study was approved by the local ethics committee and subjects gave written informed consent. Tasks and testing procedures were in accordance with institutional guidelines and the study conforms to the Declaration of Helsinki.

7.3.2 Experimental design & motor training

Subjects performed elementary thumb tapping movements on a computer keyboard during the EEG measurements. While placed in front of a height-adjustable table, their hands were positioned palm down beneath the side edges of a computer keyboard with the left thumb lying on the leftmost CTRL key and the right thumb lying on the ENTER key of the numeric keypad. Tapping movements were carried out with either the right or left thumb in convenient or maximum speed. A detailed description of the tapping task is given in Lutz et al. *(2005)*. The *Presentation* experimental software environment (Neurobehavioral Systems, Version 0.76, 2003) was used to present visual instructions for the 4 conditions and to record key presses. The motor task was delivered in a box-car design with alternating rest (OFF) and activation (ON) blocks to make it comparable to previously published fMRI studies of our group. One experimental session consisted of five OFF and 4 ON periods each lasting for 20 s. The 4 task conditions were randomly assigned to the 4 ON blocks per run. Subjects performed a total of four sessions.

The motor training consisted of fast repetitive tapping movements of the left thumb that were carried out on a daily basis for four weeks. The aim was to increase maximum tapping speed. Since tapping training was carried out on subjects' home computers, we gave careful instructions how to perform the trained thumb movement. In-house software (TapTrainer) was used to guide the daily

training sessions and to record Inter-Tap-Intervals (ITIs) as indicators for tapping speed. This allowed us to ensure that subjects accomplished the training regularly and in accordance with the instructions.

7.3.3 Statistical analysis of ITIs

ITIs derived from the TapTrainer software were analyzed using a one-way repeated measurements ANOVA with SESSION (22 factor levels) as within-subject factor. Increases of maximum tapping speed across the training were tested using trend analyses implemented in the SPSS software (http://www.spss.com). ITIs recorded during pre- and posttraining EEG experiments were subjected to a repeated measure ANOVA with TIME (pre- vs. posttraining) and RATE (convenient vs. maximum) and HAND (left vs. right) as within-subject factors. Paired-samples post-hoc t-tests were applied.

7.3.4 Acquisition of EEG data

Continuous EEG was recorded from 30 scalp electrodes (Ag/AgCl), mounted in a cap ("Easy Cap System", according to the International 10-20 system, FMS Falk Minow Services, Germany) using a Brain Vision amplifier system (Brain-Products, Germany). FCz served as reference electrode. The electro-oculogram (EOG) was recorded from two additional electrodes placed below the outer canthi of each eye. The BrainVision Recorder software (BrainProducts, Germany) was used to record the data. Electrode impedance was kept below < 10 kΩ. Data were sampled at 500 Hz, the lower and upper cut-off frequencies were 0.01 and 50Hz.

7.3.5 Preprocessing of EEG data

We used the BrainVision Analyzer software for filtering and artifact correction. To avoid the loss of collected information we ran the ICA (independent component analysis) algorithm implemented in the BrainVision software to correct for eye artifacts (eye blinks, eye movements). Individual EEG data were additionally checked for muscle artifacts by visual inspection. Artifact-free EEG material was recomputed to average reference and digitally band passed to 1.5–30 Hz. In preparation for the analysis of task-related α-power, the EEG material

was then segmented into non-overlapping epochs of 1024 data points, separately for each task condition. A minimum of 30 artifact-free trials was required for each condition. At this point, data were exported to LORETA for further analysis (BrainVision Analyzer plug-in *'ExportSegmentsForLoreta.vabs'*). The Fast Fourier Transform (FFT) algorithm implemented in the LORETA-KEY software package was applied to each single EEG sweep and the resulting cross-spectra were averaged for each subject and task condition. The frequency range of interest was set to the individual alpha frequency (see further down). Subsequently, corresponding LORETA intracerebral spectral power values were estimated.

7.3.6 Intracerebral estimation of spectral power

LORETA computes 3D distributed linear solution for the EEG inverse problem within a three-shell spherical head model registered to the Talairach human brain atlas. The solution space is restricted to Talairach cortical and hippocampal grey matter and includes 2394 voxels (7x7x7 mm resolution) each voxel containing an equivalent current dipole. LORETA solutions consist of voxel current density values (A/m^2) that is consistent with the EEG spectral power density at the scalp electrodes. The LORETA linear solution is characterized by the property that the activity at any given voxel must be as similar as possible to the average activity of its neighboring voxels. This property corresponds to the mathematical implementation of highly synchronized activity among neighboring neurons. The LORETA method has been previously validated *(for a review see Pascual-Marqui et al., 2002)*.

7.3.7 Individual frequency bands

Frequency bands were individually defined for each subject according to Klimesch et al. *(1999)*. Classically, the definition of individual alpha frequencies (IAF) is based on alpha peak detection and on eyes-closed EEG recordings, identifying the maximum power within a certain frequency range. However, most studies determining IAFs used cognitive tasks. Since the present study investigates motor behavior, the sensorimotor (mu) rhythm is focused. The mu rhythm refers to an EEG oscillation with one dominant frequency in the 10 -

15 Hz band, most prominent at electrodes over the sensorimotor cortex in the absence of movement *(for a review see Pineda, 2005)*. To ensure that the assessed frequency band is sensitive to finger movements, we defined it on the basis of the frequency showing most prominent differences in power between a resting baseline and an averaged movement condition at scalp electrodes overlying M1/S1 (C3/C4).

7.3.8 Statistical analysis of EEG data

Comparisons of the spectral power values between conditions were performed as non-parametric voxel-by-voxel t-tests which result in a t-value for each single voxel and provide threshold t-values (corrected for multiple comparisons) for $p<0.05$ and $p<0.10$ (for details see Nichols & Holmes, 2002). First, to obtain a general impression of cortical regions that show a movement-related modulation of spectral power, we compared intracortical α-power values between movement conditions [left thumb tapping at convenient (LC) and maximum (LM) speed] and a resting baseline. As the focus of the present study is placed on training-related changes in neural activity, we compared pre- and posttraining α-power values for RC and RM. In addition, RC and RM were directly compared to re-evaluate the 'rate effect'.

7.3.9 ROI analysis

Furthermore, we used the more powerful region-of-interest approach to specifically explore (a) training-related changes and (b) the rate-effect in M1. The ROI analysis was performed using an in-house Matlab routine. The left and right M1-ROIs were created based on anatomical definitions *(for details see Koeneke et al., 2004)*. In both regions, mean spectral α-power values were computed for each subject, condition and time. Due to immense intersubject variability of resting α-power levels, task-related power decreases (TRPDs; reflect regional neural activation) *(Gerloff et al., 1998)* were computed using a modified version of Pfurtscheller's ERD equation *(Pfurtscheller & Aranibar, 1977)*:

$$TRPD\% = \frac{\alpha Power_{Rest} - \alpha Power_{Movement}}{\alpha Power_{Rest}} * 100\%$$

Note that TRPDs ('more neural activity') are expressed as positive values. TRPD values were analyzed in a three-way repeated measures ANOVA with 'time' (pre- vs. posttraining) and 'rate' (convenient vs. maximum speed tapping) and 'hemisphere' (left vs. right M1) as within-subject factors.

7.4 Results

7.4.1 Behavioral results

The repeated measures ANOVA with *SESSION* as within-subject factor revealed a significant ITI reduction across training *[F(2.0, 14.2) = 4.648, p = 0.028, η^2 = 0.39]* characterized by a strong linear trend *[F(1,7) = 7.38, p = 0.03, η^2 = 0.51]*. Training effects were also observed for ITIs obtained during EEG recordings. The repeated measures ANOVA uncovered a significant *TIME* x *RATE* x *HAND* interaction *[F(1,7) = 7.22, p = 0.031, η^2 = 0.51]*. In case of maximum speed tapping, a marked reduction of ITIs from pre- to posttraining was only evident only for the trained left but not the right thumb *[left thumb: T(7) = 3.72, p = 0.007; two-tailed; right thumb: p = .64]*. For convenient-speed tapping, subjects showed faster tapping with both hands after the training *[right hand: T(7) = 2.44, p = 0.045 / left hand: T(7) = -2.55, p = 0.038; two-tailed]*.

7.4.2 LORETA-based localization of α-power

The comparison of movement conditions (LC, LM) with a resting baseline revealed reduced α-power (reflecting increased neural activation) in a widespread motor network involving M1/S1 as well as lateral and mesial premotor regions (see Figure 7.4-1A). The pattern of activation did not significantly differ between pre- and posttraining measurements. As displayed in Figure 7.4-1B, the analysis of cortical regions showing a modulation of α-power with movement rate revealed foci in the left and right primary sensorimotor cortex *[right BA4: T = 3.8, p < 0.05 / left BA4: T = 4.8, p < 0.01; $\alpha\text{-Power}_{convenient} > \alpha\text{-Power}_{maximum}$]*.

7.4.3 LORETA-based ROI analysis.

We uncovered training-related changes of neural activity when restricting the focus of analysis to M1. The three-way repeated-measures ANOVA revealed a main effect of *TIME [F(1,7) = 12.4, p = 0.01, η^2 = 0.64]*, indicating a general reduction of TRPD values across the two hemispheres and speed conditions (see Figure 7.4-1A, middle panel). However, subsequent testing shows that in case of LM, a significant reduction of TRPDs from pre- to posttraining is only

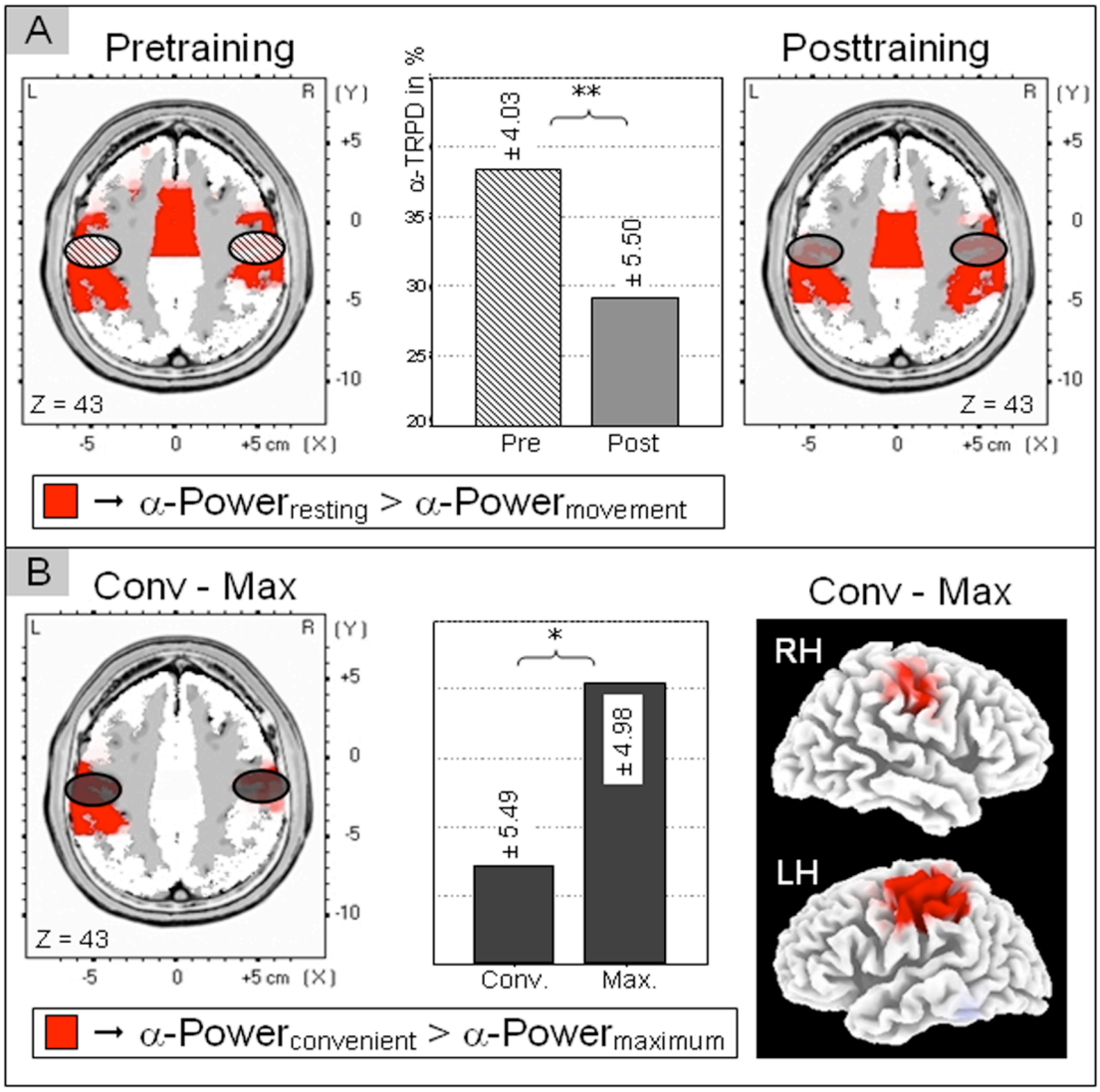

Figure 7.4-1: (A) LORETA-based intracortical localization of α-power changes. *Right and left panel:* Direct voxel-wise comparison of spectral α-power values obtained during the resting baseline and maximum-speed tapping using the left thumb. *Middle panel*: mean α-TRPD values for pre- and posttraining measures pooled across the two hemispheres and speed conditions. (B) LORETA-based intracortical localization of the 'rate effect'. *Right panel*: direct voxel-wise comparison of spectral α-power values obtained during convenient and maximum-speed tapping. *Left panel*: rate-modulated regions overlaid on a rendered standard brain. *Middle panel*: Mean α-TRPD values (baseline-corrected) for convenient and maximum-speed tapping pooled for the two hemispheres and times. [** $p < 0.01$ / * $p < 0.05$]

evident for the left hemisphere *[left M1: $T = 2.54$, $p = 0.018$, one-tailed / right M1: $p = 0.27$]*. Training-related reductions in α-power were observed bilaterally for convenient-speed tapping *[left M1: $T = 4.45$, $p = 0.002$ / right M1: $T = 2.0$, $p =$*

0.043]. In addition to training-related effects, the ANOVA exposed a main effect of *RATE [F(1,7) = 7.3, p = 0.03, η^2 = 0.51]* (see Figure 7.4-1B, middle panel).

7.5 Discussion

Behavioral data are in good agreement with previous studies *(Annett et al., 1974; Hammond et al., 1988; Jäncke et al., 1997; Aoki et al., 2003)*. As a result of intense training, the left thumb is able to meet the maximum tapping speed of its right counterpart. The size of the observed speed gain (31.6 ± 24.1 ms) resembles the reported speed gains by Peters *(1976)* who studied prolonged training of maximum tapping speed in a single case.

Previous studies using different techniques provide good evidence that the primary sensorimotor cortex is strongly involved in controlling subjects' maximum tapping speed *(Humphrey, 1972; Ashe & Georgopoulos, 1994; Jäncke et al., 1998a; Jäncke et al., 1998b; Jäncke et al., 2004)*. Assuming that maximum-speed finger tapping requires the contralateral primary motor cortex to operate at a maximum activation level, the question would be how the motor cortex implements a training-induced increase of maximum-tapping speed. In our study we uncovered that the control of the faster maximum tapping speed, as induced by training, does not demand the recruitment of additional neuronal resources in the contralateral sensorimotor cortex at post- compared to pretraining measures. Second, we revealed a decrease in neural activation from pre- to posttraining for the left hemisphere, ipsilateral to the trained hand.

The former result corroborates an earlier finding of our group showing that the amount of effort rather than the physical tapping rate determines the extent of M1 activation *(Lutz et al., 2005)* and that maximum tapping speed demands maximum M1 activation. The fact that the right M1 did not show increased activity with the behavioral speed gain strongly indicates its enhanced efficiency in controlling fast repetitive thumb movements after the training. Movement repetition in the context of longer-lasting motor sequence learning, although not widely studied, has consistently been associated with a gradually developing increase of contralateral activation (in the range of several days up to weeks) *(Pascual-Leone et al., 1994; Karni et al., 1995; Hlustik et al., 2004; Nyberg et al., 2006)*. This seems to contradict the present data at first view. However, given that motor sequence learning is a much more complex process, involving a widespread

cortical-subcortical motor network, we assume, that this type of complex motor learning might rely on different principles *(for a review see Doyon & Benali, 2005).*

The strong involvement of the ipsilateral left hemisphere in controlling effortful left hand movements is likely due to less efficient motor control functions harbored by the right hemisphere in right-handers. In line with that, it was argued that the subdominant right motor cortex would have less processing capacities to control the subdominant hand during faster finger tapping rates *(Jäncke et al., 1998a).* Specifically, the present data show a decrease of left M1 activation at post- compared to pretraining measures when maximum movement speed of the sub-dominant left hand has reached that of the dominant right hand. Therefore, we presume that the extent of ipsilateral M1 involvement is influenced by the degree of efficiency of the contralateral M1 regarding the control of a given movement.

A further aim of the present study was to replicate the classical *rate-effect* in order to further validate the LORETA method in the motor domain. LORETA-based ROI analysis showed a strongly significant *rate effect* bilaterally in M1; however, rate-related activation changes were also clearly localized to bilateral M1/S1 by means of voxel-wise LORETA comparisons of spectral power. Note that LORETA does not provide support for the evidence of rate effects in mesial premotor cortices as has been inconsistently reported before using conventional neuroimaging techniques *(Lutz et al., 2005).*

Conclusion

The main finding of the present study is a training-induced difference in maximum tapping speed of the left thumb between pre- and posttraining measures that is associated with constant levels of neural activity exhibited by the right sensorimotor cortex (contralateral to the trained left hand). In contrast, we discovered a training-related decrease of activity for the left sensorimotor cortex (ipsilateral to the trained hand). We suggest two interacting mechanisms: While the right subdominant motor cortex establishes more efficient motor control

abilities with training, the left dominant motor cortex shows strong involvement at the beginning of training – when the right-hemisphere motor system is not yet fully capable of controlling effortful subdominant-hand movements – and then progressively diminishes as the right M1 becomes more proficient.

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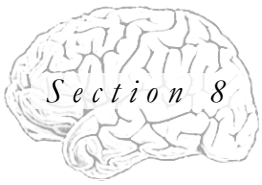

EXPERIMENT / STUDY 3

Training-induced Increases of Maximum Finger Tapping Speed Depend on the Pattern of Cortical Finger Representation.

Acknowledgements: This work was supported by an NCCR-grant to L.J. (Swiss National Foundation, Neural plasticity and repair).

8.1 Abstract

The present fMRI study reinvestigates the arrangement of cortical finger representations in the human primary hand motor area and specifically explores whether a 4-week-lasting elementary motor training changes this arrangement. The aim of the training was to increase maximum tapping speed with the subdominant thumb. We generally found extensive overlap between finger-specific representations in M1, but nonetheless identified distinct centers of activation for movements of different fingers. There was only weak evidence for a somatotopic organization of the five fingers in the homuncular sense, but strong support for an individual organization which is changed by training in an interesting manner: A) training reduced distances between finger representations and B) the smaller the distances between finger representations before training, the larger the training-induced speed gain. We conclude that a cortical organization that maximizes overlap and interlacing of neural tissue is favorable for selectively tapping a finger at maximum speed.

8.2 Introduction

The concept of somatotopy – generally referring to the organized correspondence between a cortical region and the body – evolved from electrical cortical stimulation experiments in animals and humans *(Fritsch & Hitzig, 1870; Penfield & Boldrey, 1937; Woolsey et al., 1952)* and from even earlier observations in epileptic patients by John H. Jackson *(1863)*. As a key principle of primary motor cortex (M1) organization, somatotopy is now well established as far as the functional organization of major body parts is concerned, while the controversy over the very existence of a fine-scale somatotopic arrangement within M1 subareas has been debated throughout the last decade. Most of the work conducted to resolve this question of fine-scale somatotopy has focused on the arrangement of functional finger representations in the M1 hand area.

The intimate connection between motor cortex somatotopy and the well-known schematic homunculus *(Penfield & Rasmussen, 1950)* or simiusculus figure *(Woolsey et al., 1952)* has been widely disseminated in neuroscientific text books. Unfortunately, most of these books show the figure without making reference to the original, supporting data, thus leaving the concept of the homunculus open to misinterpretation. The authors did however firmly point out in their original writings that the motor homunculus is only a cartoon with which to illustrate the gross medial-to-lateral arrangement of cortical representations of the leg, trunk, arm and face. The extent of somatotopic detail incorporated in the homunculus leaves the impression of a level of segregation of motor representations that in fact has not yet been proven and that was certainly not intended by the authors *(Schott, 1993; Indovina & Sanes, 2001)*. Interestingly, principles of convergence and divergence at a cellular level and the phenomenon of sharing neural substrate have already been observed and described in detail by Penfield and Woolsey, but these organization principles are not easily schematically represented in the context of the homunculus drawing. Despite the calls by Penfield *(1950)* and Woolsey et al. *(1952)* to exercise caution and to avoid overstretching the homunculus with unsubstantiated somatotopic detail, the idea of an orderly body map has been the starting point of many investigations de-

signed to ascertain fine-scale finger somatotopy in M1. According to the homuncular idea, the representation of the thumb would be located most lateral, anterior and inferior and the representation of the little finger would be located most medial, posterior and superior along the precentral gyrus. The remaining fingers would have a position in-between these locations. Several of the previous pertinent studies were indeed able to provide evidence in favor of a somatotopic gradient within the M1 hand area *(Kleinschmidt et al., 1997; Lotze et al., 2000; Beisteiner et al., 2001; Hlustik et al., 2001; Dechent & Frahm, 2003; Beisteiner et al., 2004)*. Importantly, many of the previous studies did only assess the locations of functional representations of two digits (in most cases, thumb or index and little finger). Finger representations have often been shown to be separable in only one or two dimensions. Generally, the distances between finger representations are small compared to the large extent of activity. Other studies have failed to demonstrate somatotopic organization at the level of finger representations *(Schieber & Hibbard, 1993; Sanes et al., 1995; Schieber & Poliakov, 1998; Volkmann et al., 1998)*. But an important observation common to all these studies – regardless of whether or not fine-scale somatotopy has been reported – is the extensive overlap between single finger representations. It is not only the overlap that is extensive: Patches of activity associated with the movement of one finger have been reported to be distributed throughout the entire M1 hand area *(for a review see"Schieber & Santello, 2004)*. Searching for an explanatory link between structure and function, Sanes (2001) proposed that *"M1 likely functions to bring together, not to separate, functionality across a limb's joints"* (page 937) *(Sanes & Schieber, 2001)*. The human hand motor skills are based on simultaneous use of different hand muscles in rapidly changing combinations, thus, a pattern of intermingled_representations might be best suited to support manifold between-finger-interactions.

It has already been shown that the arrangement of finger representations is sensitive to the effects of neural plasticity. In a study with proficient violin players, Elbert et al. *(1995)* demonstrated larger distances between the centroids of finger representations in the primary somatosensory cortex of the right hemisphere contralateral to the left hand, which receives immense sensory input dur-

ing violin playing *(Elbert et al., 1995)*. Using MEG, Volkmann et al. (1998) reported larger distances between dipole sources for different hand movements in the dominant compared to the subdominant M1 *(Volkmann et al., 1998)*. Given the effect of enlarged motor and somatosensory hand representations in S1 and M1 due to life-long training, it appears that finger representations gradually move apart when taking over more cortical space. A recent study by Hlustik et al. (2004) investigated movement representations during hand skill acquisition over the course of three weeks. However, changes in the arrangement of finger representations in four fMRI sessions accompanying skill learning were not reported despite the increasing volume of activation associated with performance gains through training *(Hlustik et al., 2004)*. Generally, the effects of longer-lasting motor training (mostly motor skill learning) in the sensorimotor system have been studied intensively using different techniques and training protocols, but in most cases the focus has been placed on the strength and extent of activation *(Pascual-Leone et al., 1994; Karni et al., 1995; Jäncke et al., 2000c; Hlustik et al., 2004; Nyberg et al., 2006)*.

In summary, the question of practice-induced changes in the arrangement of functional finger representations has received little attention so far, and the few studies that have addressed this issue have provided inconsistent results. Thus, in addition to providing a description of fine-scale cortical finger representations within M1, the present study seeks to answer the question, whether the extensive, long-lasting training of a specific elementary tapping movement changes the arrangement of these cortical finger representations.

8.3 Methods

8.3.1 Subjects

8 healthy, young subjects (6 female; age span: 22 – 28 years) without any history of neurological or psychiatric disorders took part in the study. Handedness was assessed using the Annett Handedness Questionnaire (AHQ) *(Annett, 1970)* and the hand dominance test (HDT) *(Steingruber, 1971; Jäncke, 1996)*. According to these tests, all subjects were classified as consistent right-handers. The study was approved by the local ethics committee. Each individual gave written informed consent. Tasks and testing procedures were in accordance with institutional guidelines and the study conforms to the Declaration of Helsinki (the code of ethics of the world medical association).

8.3.2 Task design

The motor task consisted of elementary repetitive tapping movements performed at maximum speed using each finger separately. Subjects were carefully instructed before the fMRI session in how to carry out the tapping movements in order to ensure maximally individuated finger movements. Subjects performed a total of two runs – one run per hand. The order of the runs was pseudo-randomized across subjects. The fingers of the hand indicated for use during a particular run rested on 5 buttons fixed on a plastic board. To provide a comfortable position for the fingers the button arrangement was individually adapted. It should be pointed out that the subjects were trained intensively to achieve a comfortable fingers position in order to avoid cramps or too much co-contraction of the non-involved fingers. These limitations may have led to some reduction of maximum tapping speed. The experiment was designed using a classical fMRI box-car design with alternating rest (20 s) and activation (20 s) blocks. Visual Stimulation – needed to guide the motor task - was presented via a video projector onto a translucent screen that subjects viewed inside the scanner via a mirror. Two hands were presented in the middle of a black screen. In order to avoid spatial transformation processes subjects saw the back of the hands. The finger that had to be used for tapping during one particular ON

block was highlighted by red color for the whole duration of the ON block. Each finger was pseudo-randomly assigned to two ON blocks during the course of one run consisting of 10 ON blocks in total. During the OFF-blocks, no finger was highlighted and subjects were instructed to strictly refrain from moving the fingers at those periods. Subjects took part in two fMRI sessions, one before and the second after a four-week motor training (see below for details) using the same motor task.

8.3.3 Scanning procedure

Functional magnetic resonance imaging was performed on a Philips Intera 3T whole-body MR unit equipped with a commercial eight-element head coil array (*MRI Devices Corporation, Waukesha WI, USA*). Three-dimensional anatomical images of the whole brain were obtained by using a T1-weighted three-dimensional, spoiled, gradient echo pulse sequence (TR = 20 ms, TE = 2.30 ms, flip angle = 20°, FOV = 220×220, acquisition matrix = 224×224, voxel size = 0.98mm × 0.98mm × 0.75 mm3, 180 slices, slice thickness 0.75mm).

Functional data were obtained from 6 transverse slices using high-resolution single-shot EPI technique with SENSE R=2.7 *(Pruessmann et al., 1999)* (TR = 2000 ms, TE = 35 ms, flip angle = 75°, FOV = 180×180, acquisition matrix = 80×80, voxel size = 0.94mm × 0.94mm × 4.0mm, slice thickness 4.0mm). The six slices were manually placed to cover the hand motor knob, a structure that has previously been suggested to house functional finger representations within M1 *(Yousry et al., 1997).*

8.3.4 Data analysis

Image analysis was performed on a PC using SPM2 (http://fil.ion.ucl.ac.uk/spm) running on MATLAB 5.3 (*Mathworks Inc., Natiek, MA, USA*). In order to correct for motion artifacts all images recorded during pre- and posttraining fMRI sessions were realigned to the first volume of the first pretraining run. A Gaussian kernel of 1.5mm full-width-at-half-maximum was applied to smooth the data. Activated voxels were identified using the "General Linear Model" approach. A statistical model for each subject was

computed, applying a box-car model, convolved with a standard hemodynamic response set and eliminating low-frequency noise. Single-subject models included pre- and posttraining sessions. A statistical parametric map of the T-statistic was generated for each voxel to test hypotheses about regionally specific condition effects. Linear contrasts were employed for each subject and condition, as suggested by Friston et al. (1995). We specifically compared functional MR images recorded during repetitive tapping movements of each individual finger with those recorded during the non-movement baseline condition, resulting in five baseline contrasts [*D1 (thumb) > Rest, D2 > Rest, D3 > Rest, D4 > Rest, D5 (pinky) > Rest*] for each hand and time point of measurement [*pretraining, posttraining*]. The resulting set of voxel values for each contrast yields a statistical parametric map of the T-statistic [*SPM(T)*].

8.3.5 Regions-of-Interest analysis

Given that we only acquired 6 slices covering mainly M1, we consequentially restricted the analysis of functional MR images by using a region-of-interest (ROI) approach. In a first step, the individual T1-weighted anatomical image was coregistered to the SPM(T)-images which resulted from calculating baseline contrasts as described above. Thereafter, the coregistered anatomical image was used to individually create anatomical ROIs for both hemispheres using MRIcro 1.4 (www.mricro.com). Anatomical ROI definitions were selected according to earlier studies *(Roland & Zilles, 1996; Fink et al., 1997)*. Finally, SPM(T)-images resulting from single-subject analyses were subjected to ROI statistics. An in-house MATLAB tool was employed to compute the center of mass (COM) of the activation map for each individual M1-ROI and baseline contrast using Equation 1.

Equation 1:

$$COM = \frac{\sum_{i=1}^{n} t_i s_i}{\sum_{i=1}^{n} t_i}$$

where s denotes the coordinate vector and t the t-value at each of the n voxels belonging to a given ROI. Only voxels carrying a positive t-value were included

in the computation. Deactivations, represented by negative t-values, would conversely affect the sum vector, and thus, contaminate results.

We used the COM as an estimator for the point of main activation rather than the strongest activated voxel. Lotze et al. *(2000)* suggested that this parameter is less sensitive for random fluctuations of the MR signal and signal-to-noise variations *(Lotze et al., 2000)*. The calculation of the COM was not restricted to certain significantly activated clusters since multiple clusters were found to be statistically significant in some of the baseline contrasts. Boundaries of such clusters are determined using arbitrary statistical cutoff value, thus, making the size of the included region sensitive to statistical factors like power, sensitivity and specificity of the used method. With the inclusion of all M1 voxels showing a positive effect, we expect more stable results

2d-distances. Because one of the aims of the current study is to reassess the issue of fine-scale arrangement of finger representations with respect to the homuncular idea, we subsequently performed a transformation of original COM coordinates into stereotactic reference space, however, restricting normalization to linear algorithms. This allowed us to calculate simple differences between finger-specific COM coordinates separately along the 3 axes (anterior-posterior, lateral-medial, and inferior-superior). In the case of high variability of the arrangement of two finger representations in a particular dimension (X, Y or Z), individual difference values would accumulate around zero (e.g. when 50% of the subjects have the thumb representation located anterior to the index finger location, and the other 50% show the opposite pattern). Thus, hypothetically, when studying the relation of thumb and index finger representations on the right hemisphere, a positive difference in x-dimension would indicate that the thumb is located lateral to the index finger consistently across subjects. Differences were tested for significance using one-sample t-tests with a test value of zero.

3d-distances. In a second kind of analysis, we determined Euclidian distances, which provide information about absolute distances between finger-specific

COM coordinates. Applying this strategy of analysis, we evaluated whether the COMs of two particular finger representations have locations that are significantly different from each other regardless of a particular somatotopic arrangement. This way, we take interindividual differences in somatotopic arrangement in account when assessing training-related changes. Differences were tested for significance using one-sample t-tests with a test value of zero.

To study training effects, Euclidian distances were preferred over direction-sensitive two-dimensional distances because the data did not substantiate a consistent somatotopic organization within the M1 hand area, instead showing high variability between individual subjects. Since the motor training was performed with the thumb of the subdominant left hand, we calculated the mean distance between the thumb and remaining fingers (→ equation 2) for pre- and post-training measurements.

Equation 2:

$$\Delta_{D1} = \frac{d_{(D1-D2)} + d_{(D1-D3)} + d_{(D1-D4)} + d_{(D1-D5)}}{4}$$

This enabled us to assess whether the thumb representation specifically changes in relation to the remaining fingers as a result of its extensive training. Pre- and posttraining values were compared using t-tests for paired samples. Considering convergence and divergence phenomena in M1 organization and the resultant strong overlap of finger representations, we further determined a parameter estimating the distribution (D) of the entire hand representation by adding up the distances between all possible finger pairs. This parameter would account better for global training effects. We additionally calculated the mean extend (E) of the functional hand motor representation (→ equation 3).

Equation 3:

$$E = d_{(D1-D2)} + d_{(D2-D3)} + d_{(D3-D4)} + d_{(D4-D5)}$$

For both, specific (Δ_{D1}) and global (D, E) parameters, pre- and posttraining values were compared using t-tests for paired samples.

8.3.6 Motor training & behavioral data analysis

The motor training consisted of elementary, repetitive movements performed with the left thumb (tapping on a key) and was accomplished on 6 days per week for the duration of four weeks. The subjects were instructed to aim at increasing maximum tapping speed. After the pre-training fMRI session, subjects were precisely instructed in how to carry out the motor training. They were told to put the right hand beneath the computer keyboard with the thumb lying on the *CTRL* key of the numeric keypad and to rest the remaining digits aside. Subjects were further advised to only involve the thumb during the tapping periods and to prevent the other digits from moving. One daily training session consisted of 30 consecutive trials each of which comprised a movement execution period (20 sec) and a resting period (40 sec). The tapping training was carried out by the subjects on their home computers. In house software (*Tap-Trainer*) was used to guide the daily training sessions and to record particular training parameters, for example, Inter-Tap-Intervals (ITIs) as indicators of tapping speed. This gave us the opportunity to track the course of training. We were therefore able to ensure that subjects accomplished the training regularly and in accordance with the instructions. To control whether or not subjects did profit from training and gained speed we calculated mean ITIs for each training session/day and further analyzed these mean values using a repeated measures ANOVA with session number as within-subject factor. Greenhouse-Geisser corrections for degrees of freedom were used to correct for possible violations of homoscedasticity *(Keselman et al., 2001)*. We additionally determined mean ITIs for the beginning and for the end of training by averaging the recorded ITIs for the first three as well as for the last three training sessions for each individual separately. These mean ITIs were compared using paired t-tests.

During the fMRI sessions, ITIs were registered by recording button presses. To test for overall performance differences between fingers (across both hands and time points) data were subjected to a repeated measures ANOVA with 'digit' (D1 – D5), 'time' (pre- vs. posttraining) and 'hand' (left vs. right) as within-subject factors. Subsequent paired-samples t-tests were performed to quantify differences. Where it was useful the effect size according to Cohen *(1988)* was

calculated. Cohen's d was determined as the difference between two means divided by the pooled standard deviation. The pooled standard deviation is the square root of the average of the squared standard deviations *(Rosnow & Rosenthal, 1996)*. According to Cohen, an effect size of $d > 0.5$ is considered moderate, while $d > 0.8$ is considered to be large *(Cohen, 1988)*.

8.4 Results

8.4.1 Behavioral data

Finger-specific tapping rates during fMRI. Three-way repeated measurements ANOVA of mean tapping rates revealed significant main effects for *digit* [$F(1.7,8.5) = 5.931$, $p = 0.027$, $\eta^2 = 0.54$], *time* [$F(1,5) = 7.885$, $p = 0.038$, $\eta^2 = 0.619$] and *hand* [$F(1,5) = 7.795$, $p = 0.038$, $\eta^2 = 0.609$], with a decrease in ITIs from pre- to posttraining, and with generally smaller ITIs for the dominant right compared to the subdominant left hand. Comparing ITIs between thumb and index finger in more detail revealed clear differences ($ITI_{Thumb} > ITI_{Index}$) in pretraining measures for both hands [*right hand:* $T(5) = 3.248$, $p = 0.023$; *left hand:* $T(5) = 5.327$, $p = 0.003$], while differences between the two fingers were neutralized after training [*right hand:* $T(5) = 1.635$, $p = 0.163$; *left hand:* $T(5) = -.756$, $p = 0.484$]. Further differences between pre- and posttraining were found in the left hand for all fingers except the index finger (figure 1 for details).

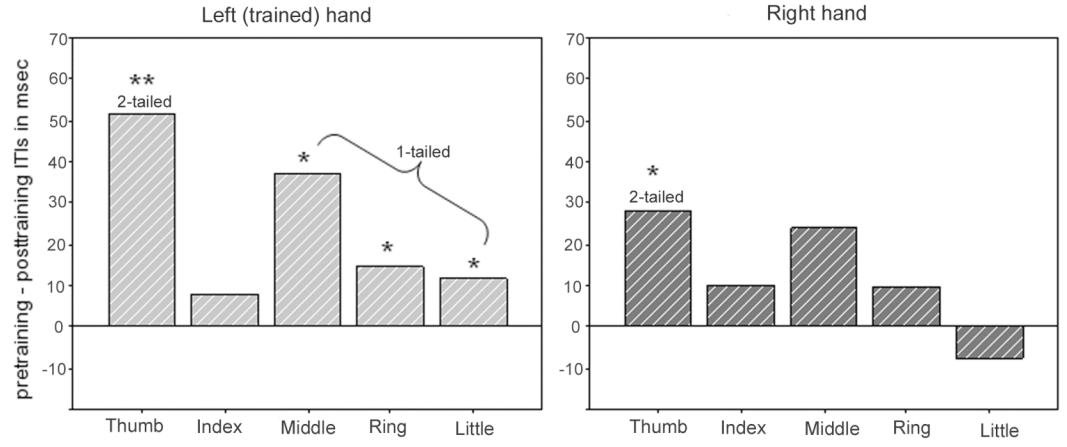

Figure 8.3-1: Training-related decrease of Inter-Tap-Intervals (ITIs) in msec, separately for all fingers of the right and left hand. Data refer to ITIs recorded during the fMRI sessions. Bars represent the difference in ITI between pre- and posttraining measurements.

Training Data. Subjects performed 23.50 ± 0.76 training sessions on average (range: 22 – 24). Subjecting mean ITIs obtained for 22 training sessions to the repeated measures ANOVA revealed a significant training effect [$F(2.0,14.2) =$

4.648, p = 0.028, η^2 = 0.39]. Subsequently conducted trend analyses revealed a strong linear trend [*F(1,7) = 7.38, p = 0.03, η^2 = 0.51*] with strongly decreasing ITIs during the course of training (Figure 2). In addition to the trend analysis, the comparison of the mean ITIs of the first and last three training sessions revealed a significant decrease of the ITIs after two weeks of training [*T(6) = 2.75, p = 0.029*].

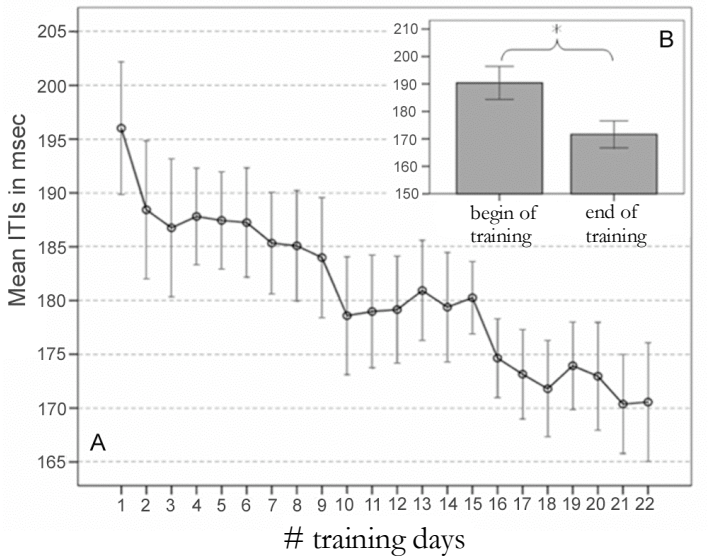

Figure 8.3-2: Inter-Tap-Intervals (ITIs) in msec as recorded by the Tap-Trainer Software. (A) Decrease of ITIs throughout 4 weeks of left-thumb tapping training. (B) Averaged ITIs for the first three training sessions (= pretraining) and for the last three training sessions (= post-training). Error information is given as S.E.

8.4.2 Neurophysiological data: The arrangement of finger representations before training

Finger-specific activation volumes. The volume of activation for each baseline contrast [finger tapping vs. resting baseline] was determined by counting the number of voxels positively correlated with the task design. Statistical testing ($p < 0.05$) did not reveal any differences between the fingers before training. Activation volumes were determined from single-subject analyses performed on non-normalized brain scans.

Euclidian distances between finger-specific COM coordinates. Mean Euclidian distances between all possible finger pairs were computed after transferring the data into stereotactic space. Before training, the smallest distance was 1.07 ± 0.33 mm measured between representation centers of the left thumb and middle finger on the right hemisphere, while the largest distance was found

between index and little finger on the right hemisphere (3.55 ± 1.32 mm). Except for 3 of the 20 comparisons (10 finger pairs per hand), the null hypothesis (distances are not significantly different from zero) was rejected in all cases, based on a significance level of 1%; the remaining 3 cases did survive a significance threshold of 5%. Mean distances, T- and p-values for all finger pairs are listed in Tables 8.3-1 and 8.3-2, respectively for the right and for the left hand.

Table 8.3-1: Euclidian Distances between finger-specific representations of the right hand in the left hemisphere M1 - One-Sample Tests [Test Value = 0]

	Right Hand at PreTraining (left M1)				Right Hand at PostTraining (left M1)			
	Mean Difference	T	df	p	Mean Difference	T	df	p
Thumb-Index	1.68	4.93	7	.002	2.40	2.91	7	.023
Thumb-Middle	1.07	5.86	7	.001	2.29	3.73	7	.007
Thumb-Ring	1.69	5.55	7	.001	2.46	2.82	7	.026
Thumb-Little	2.16	3.84	7	.006	2.75	3.36	7	.012
Index-Middle	1.79	3.78	7	.007	1.16	5.90	7	.001
Index-Ring	2.34	4.25	7	.004	1.88	3.96	7	.005
Index-Little	2.62	3.49	7	.010	1.35	6.06	7	.001
Middle-Ring	1.36	4.74	7	.002	1.63	2.78	7	.027
Middle-Little	2.37	4.07	7	.005	1.20	5.67	7	.001
Ring-Little	2.06	3.80	7	.007	1.52	3.02	7	.019

Table 8.3-2: Euclidian Distances between finger-specific representations of the left trained hand in the right hemisphere M1 - One-Sample Tests [Test Value = 0]

	Left Hand at PreTraining (right M1)				Left Hand at PostTraining (right M1)			
	Mean Difference	T	df	p	Mean Difference	T	df	p
Thumb-Index	2.72	7.04	7	.000	1.99	3.62	7	.009
Thumb-Middle	2.64	4.99	7	.002	2.06	3.63	7	.008
Thumb-Ring	2.41	3.18	7	.016	1.73	4.97	7	.002
Thumb-Little	3.08	3.59	7	.009	1.70	5.45	7	.001
Index-Middle	2.41	5.44	7	.001	0.93	7.83	7	.000
Index-Ring	2.24	6.18	7	.000	1.67	5.87	7	.001
Index-Little	3.55	3.77	7	.007	2.09	6.21	7	.000
Middle-Ring	2.26	7.63	7	.000	1.61	5.48	7	.001
Middle-Little	3.12	3.19	7	.015	1.89	5.59	7	.001
Ring-Little	3.24	2.61	7	.035	1.21	4.57	7	.003

Table 8.3-3: Distances between finger-specific COM coordinates separately along the 3 axes for the left hand (right M1) before training - One-Sample Tests [Test Value=0]

		X-Dimension			Y-Dimension			Z-Dimension		
	df	T	p	Mean Diff.	T	p	Mean Diff.	T	p	Mean Diff.
Thumb-Index	7	0.01	.989	0.01	0.50	.636	0.21	-1.37	.214	-0.71
Thumb-Middle	7	1.71	.130	1.22	1.41	.202	0.81	-2.35	.051	-0.63
Thumb-Ring	7	0.88	.409	0.78	2.60	.036	1.02	-0.03	.975	-0.02
Thumb-Little	7	3.21	.015	1.68	3.34	.013	1.36	-1.91	.098	-1.53
Index-Middle	7	2.50	.041	1.20	2.85	.025	0.60	0.12	.910	0.08
Index-Ring	7	1.45	.191	0.77	3.23	.014	0.81	1.36	.216	0.69
Index-Little	7	1.40	.206	1.67	3.14	.016	1.15	-1.27	.244	-0.82
Middle-Ring	7	-0.75	.481	-0.44	0.66	.533	0.20	1.14	.293	0.61
Middle-Little	7	0.48	.649	0.47	1.15	.289	0.55	-0.92	.388	-0.90
Ring-Little	7	0.79	.458	0.90	1.11	.306	0.35	-1.40	.203	-1.51

Assessment of somatotopic arrangement. Since somatotopic arrangement cannot be assessed directly by means of Euclidian distances due to a lack of direction information (an Euclidian distance between two fingers does not carry information with respect to, e.g., which of the two finger representations is located more anterior, lateral and inferior compared to the other), we additionally related finger-specific COM coordinates to each other by calculating COM differences between finger representations along the 3 axes (anterior-posterior, lateral-medial, inferior-superior). Corresponding data (mean distances, T- and p-values) for the left trained hand (right M1) are provided in table 8.3-3. First of all, our data do not prove/support the existence of an unambiguous somatotopic ordering of finger representations within the M1 hand area. Generally, as one-sample t-tests demonstrate, there is a clear separation of finger-specific representations at pretraining measures in both hemispheres (related results are presented below).

Finger-specific COM coordinates for the right hemisphere, contralateral to the trained left hand, are depicted in Figure 3 and show significant differences as marked by connecting lines. Before training, 9 difference values derived from the right hemisphere (X: 1/10 differences; Y: 4/10; Z: 4/10) and 9 difference values derived from the left hemisphere (X: 2/10 differences; Y: 5/10; Z: 2/10) differed significantly from zero at a significance level of 5%. Interestingly, all differences that reached significance did so in accordance with the homunculus mentioned above.

8.4.3 Neurophysiologic data: Effects of training

Finger-specific activation volumes. The training did not induce any significant changes in the volume of neural activity associated with the tapping movement of any single finger ($p > 0.05$).

Distances between finger-specific COM coordinates. Visual inspection of the data (see Figure 3) strongly indicates decreased distances between finger-specific cortical representations at posttraining measures. The detailed analysis of distances between finger-specific COM coordinates along the 3 axes for posttraining fMRI data reveals that only the distance *index – middle finger* (Z-dimension) on the left hemisphere and *thumb – ring finger* (Y-dimension) on the right hemisphere survived a significance threshold of 5%. Corresponding data (mean distances, T- and p-values) for the left trained hand (right M1) at posttraining measurements are provided in Table 8.3-4. Euclidian distances between finger-specific representation maxima are also markedly reduced, although still significantly different from zero at a significance level of 5% (see tables 8.3-1 and 8.3-2). Three different parameters (dependent variables), all relying on Euclidian distances, have been determined to specify the degree of segregation of finger-specific representations.

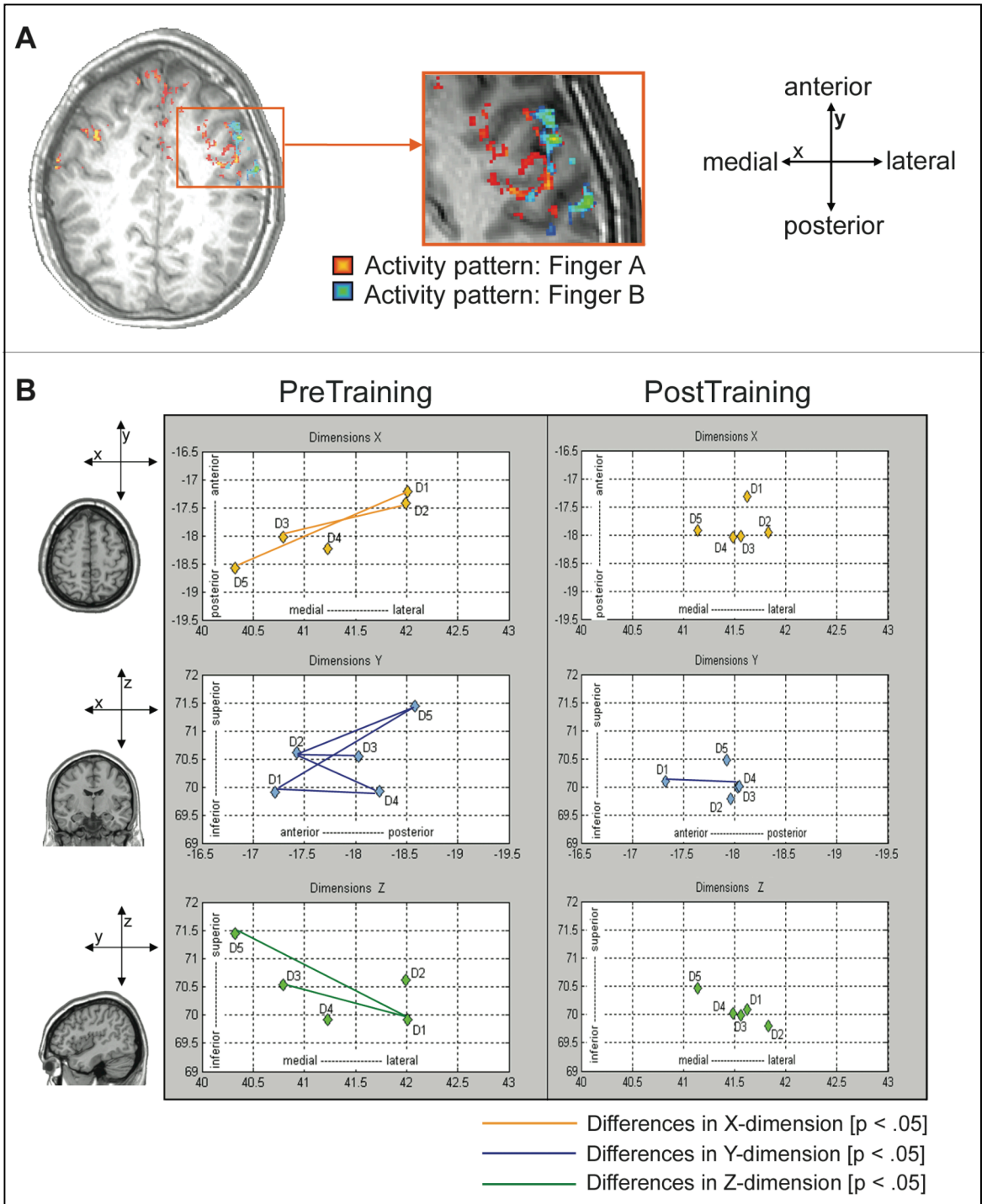

Figure 8.3-3: Arrangement of Finger-specific cortical representations the right-hemispheric M1 hand area. (A) Functional activation in the M1 hand motor region during tapping with the left index (red / orange color scale) or little (blue/green color scale) finger in a single subject. These functional activation maps were used to calculate finger-specific center-of-mass (COM) coordinates displayed in (B) for pre- (left panel) and posttraining (right panel) measurements. For reasons of comprehensibility, we display only two dimensions at a time (upper row: X-Y, middle row: X-Z, lower row: Y-Z). Significant distances between two given finger-specific COMs are marked by means of colored lines.

The comparison of the mean extent of the cortical finger representations before and after training (E), reveals a strong, significant effect of training for the right hemisphere and left-hand tapping *[T = 2.8; p = .028, two-tailed, d = 1.24]*. As can be seen from Figure 4, this effect is due to smaller distances between adjacent digits after training *[preTraining: 10.6 ± 4.9 mm; posttraining: 5.7± 2.53 mm]*.

Table 8.3-4: Distances between finger-specific COM coordinates separately along the 3 axes for the left hand (right M1) after training - One-Sample Tests [Test Value=0]

	X-Dimension				Y-Dimension			Z-Dimension		
	df	T	p	Mean Diff.	T	p	Mean Diff.	T	p	Mean Diff.
Thumb-Index	7	-0.29	.778	-0.21	1.33	.226	0.64	1.15	.289	0.30
Thumb-Middle	7	0.09	.933	0.06	1.43	.197	0.71	0.31	.769	0.10
Thumb-Ring	7	0.26	.805	0.14	3.06	.018	0.72	0.22	.833	0.08
Thumb-Little	7	1.29	.240	0.49	1.64	.146	0.60	-1.04	.335	-0.37
Index-Middle	7	1.36	.216	0.27	0.47	.656	0.07	-0.82	.440	-0.20
Index-Ring	7	0.70	.506	0.34	0.30	.774	0.09	-0.60	.565	-0.22
Index-Little	7	1.31	.233	0.69	-0.12	.912	-0.04	-1.51	.176	-0.68
Middle-Ring	7	0.15	.887	0.07	0.04	.967	0.01	-0.07	.945	-0.02
Middle-Little	7	0.77	.469	0.42	-0.36	.727	-0.11	-1.18	.276	-0.48
Ring-Little	7	1.15	.286	0.35	-0.50	.635	-0.12	-1.65	.144	-0.45

Consideration of all possible between-finger distances (parameter *D*) does also show a similar effect, though this does marginally miss the significance threshold *[T = 2.1; p = .079, two-tailed, d = 0.97]*. There were no changes for the left hemisphere with right-hand tapping for either of the two parameters.

Paired samples t-tests to compare pre- to posttraining values of the mean distance between the thumb and remaining fingers separately for each hemisphere did not reveal a significant change, this because of high interindividual variance. [*T = 1.098; p = .308, two-tailed*].

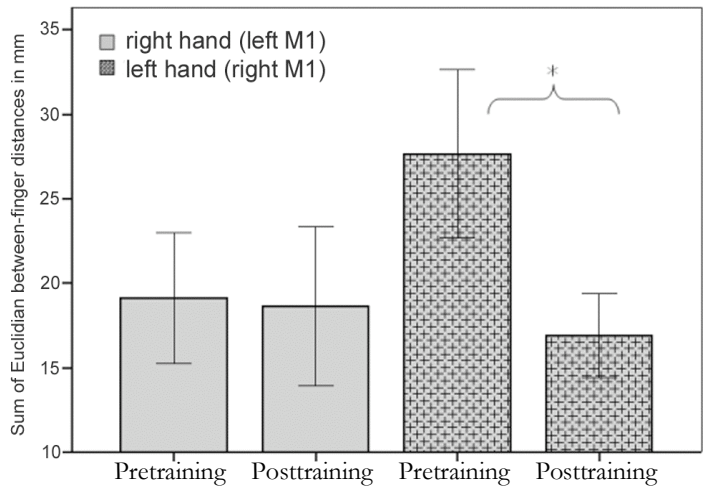

Figure 8.3-4: Mean Sum of Euclidian between-finger distances across subjects for both hands and time points of measurement. Error information is given as S.E.

8.4.4 Post-hoc correlation of behavior and neuronal activity

In order to further explore the observed effect of a training-related enhancement of overlap of cortical finger representations, we correlated behavioural data with corresponding neural activation in the right M1 hand area. Specifically, we explored separately for each of the three dependent variables (pretraining – posttraining in mm) bivariate correlations (one-sided testing) between training-related changes of tapping speed ($ITI_{pretraining}$-$ITI_{posttraining}$ in msec) and changes in distances between finger-specific COMs. As displayed in Figure 5a, correlation analysis revealed a negative correlation between the size of reduction in between-finger distances and the size of training gains in tapping speed. This is true for both global parameters, *E [r = .662; p = 0.037, one-sided, d = 1.77]* and *D [r = .683; p = 0.031, one-sided, d = 1.87]*. In addition, the magnitude of pretraining distances between finger-specific M1 representations tends to predict the amount of behavioral training gain. This relation was revealed for the mean distance between thumb and remaining fingers *[Δ_{D1}:T = -2.182; p = .072]* but also for the global distribution parameter D *[T = -2.083; p = .082]* (see Figure 5b). Specifically, correlation data show that subjects showing widely-spaced finger representations before training exhibit smallest changes in tapping speed, while the same subjects exhibit largest decreases of the distances between finger

representations. In contrast, subjects with relatively small distances between finger representations before training show almost no further reduction in distances, but they do exhibit strong speed gains in tapping.

8.5 Discussion

The current study was designed to investigate whether the somatotopic finger arrangement within the M1 hand area changes as a consequence of specific extensive training of thumb tapping speed. In fact, we found marked decreases in three-dimensional distances between finger-specific activation centroids (COMs) in the right M1 hand area contralateral to the trained hand following thumb tapping training. The reduced distance between COMs together with the absence of any change in size of the activated area indicates an increase in overlap of finger representations after training. Interestingly, we also uncovered a strong correlation between the magnitude of changed between-finger distances and the amount of behavioural gain. As a further finding - reassessing the issue of fine-scale somatotopy within the M1 hand area - our data do not provide strong support for the homuncular idea of finger arrangement. There is immense overlap of finger representations, although activation centroids for separate fingers are located at significantly different positions within the M1 hand area. In the following, we will first discuss the motor paradigm and the training-related findings before discussing the neurophysiological data and how the data relate to the current literature.

8.5.1 Behavioral data: Tapping speed and training-related changes

The tapping data revealed three main findings: (1) the maximum tapping rate varies enormously depending on the finger used for tapping; (2) tapping rates are generally faster for the dominant right hand, and (3) tapping training results in faster tapping, not only for the trained finger but also for several other fingers. Even fingers of the non-trained hand showed speed gains. Some of these finding are in good agreement with earlier behavioural studies, while other findings are new. In earlier studies, it has already been shown by many researchers that the dominant hand taps faster than the non-dominant hand *(Annett et al., 1974; Peters, 1976; Hammond et al., 1988; Jäncke et al., 1997)*. Between-finger differences in tapping capabilities, similar to those shown here, have been reported before and were attributed to training and physiological and anatomical constraints, these resulting in enslaving effects *(Schieber & Hibbard, 1993; Zatsiorsky*

et al., 2000; Aoki et al., 2003). Training-induced increases in finger tapping speed have been reported previously in highly skilled musicians *(Jäncke et al., 1997; Aoki et al., 2005)*. The amount of speed gain found in the present study resembles that reported by Peters (1976) who studied prolonged training of maximum tapping speed in a single subject. Interestingly, we observed an increase in tapping speed also for the thumb of the untrained right hand, suggesting a highly specific transfer effect from the left to the right hand. Former studies have repeatedly shown that the dominant M1 is involved in motor performance *(Kim et al., 1993; Alkadhi et al., 2002b; Kobayashi et al., 2003; Verstynen et al., 2005)* and motor learning *(Halsband, 1992; Schulze et al., 2002)* when using the right and left hand indicating some amount of interhemispheric transfer. In general, our data indicate the efficacy of the training: the motor system is able to conduct a faster tapping rate after training.

8.5.2 Arrangement of finger representations in M1 before training

We find finger-specific COM coordinates to be located at different spots within M1. Euclidian distances between single finger representations varied between 1.07mm ($D1_1$-D_3 left M1) and 3.54mm (D_2-D_5, right M1) before training. These results corroborate those of previous studies. Using fMRI, Beisteiner et al. *(2001)* reported a distance of 2.5mm between index and little finger, which is very similar to the mean distances of 2.62mm and 3.55mm (for the left and right hemisphere, respectively) revealed in our study. A more recent MEG study of the same group showed the little finger dipole to be located 2.3mm superior to the thumb dipole *(Beisteiner et al., 2004)*. Other studies have shown between-finger distances of similar extent *(Hlustik et al., 2001; Dechent & Frahm, 2003)*. One fMRI study by Lotze et al. *(2000)*, however, found clearly larger 3d-distances between fingers (D1 – D2 = 9.2mm). This discrepancy might result from differences in the movement paradigm, which underlies the determination of functional finger representations. In addition to these differences, differences in fMRI parameters and, without doubt, differences in analysing strategies might play a role here. In summary, small though significant location differences between finger-specific centroids combined with strong overlap indicate a strongly intermingled architecture of the functional hand motor representation

that underlies the neural control of highly complex and proficient finger movement.

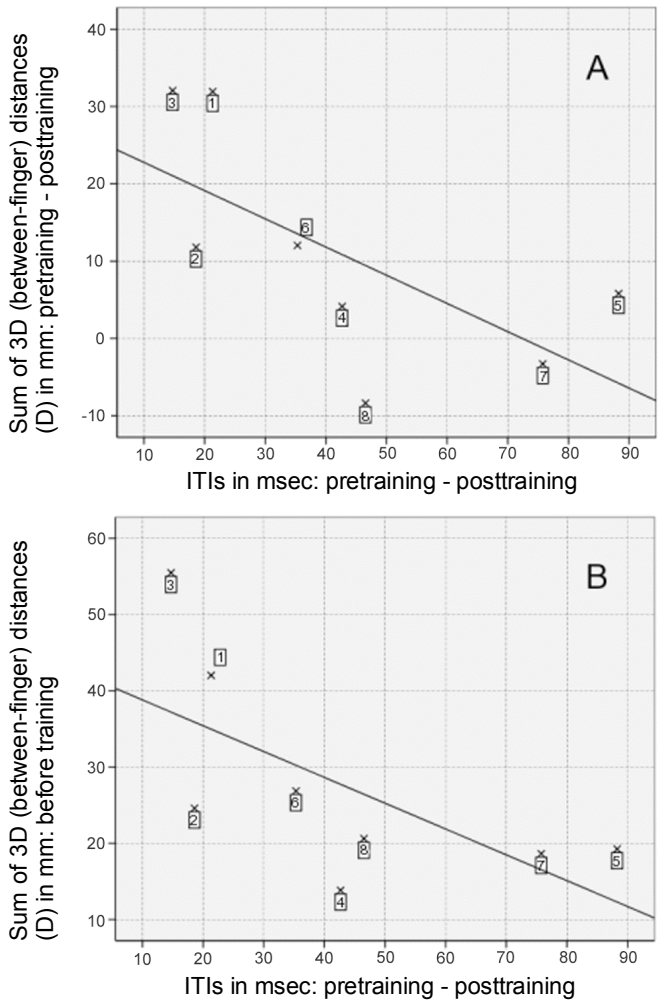

Figure 8.3-5: Correlation between behavioral and neurophysiological data. (a) Correlation between speed gains and the amounts of decreases in between-finger distances (parameter D: sum of all between-finger distances). (b) Prediction of the size of speed gains by the extent of segregation of finger representations before training

Penfield & Boldrey *(1950)* introduced the concept of the well-known motor homunculus in the middle of the last century. Though not explicitly intended to illustrate so much detail, the homuncular figure also included information about fine-scale somatotopy within the hand-motor area, with the thumb being located most lateral, inferior and anterior and the other fingers arranged along the central sulcus. Many studies have been designed to test the idea of fine-scale

somatotopy, using modern neuroscientific methods such as fMRI, PET and MEG. However, the presented results are inconsistent. Most of the studies report strong overlap between the representations of single fingers. Our data do not indicate a clear somatotopic arrangement. Neither single-subject nor group analyses consistently localize all finger-specific COMs in the way proposed by Penfield & Boldrey *(1950)* or Woolsey et al. *(1951)*. However, the assessment of finger somatotopy across subjects separately along the three axes revealed some consistent between-finger relations, at least before training. Interestingly, in cases where one finger was consistently located anterior, inferior or lateral to the second finger of a given pair, the relationship proved to coincide with the order predicted by the homunculus model. This finding is in agreement with many previous studies reporting somatotopic gradients. It must be taken into consideration that most of these studies only analyzed data pertaining to 2 or 3 fingers *(Beisteiner et al., 2001; Hlustik et al., 2001; Beisteiner et al., 2004)*. There is only one study to date that reports a clear ordering of all 5 fingers using fMRI *(Dechent & Frahm, 2003)* and this was achieved by considering only non-overlapping voxels. More importantly, there is no study showing somatotopic arrangement in all 3 spatial dimensions. Our findings are in line with previous studies that question fine-scale homuncular architecture *(Schieber & Hibbard, 1993; Sanes et al., 1995)*. These studies reported widely distributed activation throughout M1 irrespective of the finger that was moved by the subjects. In fact, single-cell studies in monkeys have shown that a given M1 neuron is active with individuated movements of multiple fingers, suggesting that each of those movements is achieved by the activity of highly overlapping neuronal populations *(Schieber & Hibbard, 1993)*. From the few cases of patients suffering from circumscribed, focal lesion in the primary motor cortex, it is generally understood these small lesions do not affect single fingers exclusively. Nevertheless, there is little evidence for a greater representation of movements of radial fingers laterally and ulnar fingers medially. The same negative findings resulted from injections of muscimol *(Schieber & Poliakov, 1998; Brochier et al., 1999)*. Thus, the alternative approach of somatotopic gradients seems to provide a much better explanation for our data as well as empirical data from previous studies. This approach makes two main assumptions a quantitative dominance

of finger-specific neurons at certain locations within the M1 hand area, and a high degree of overlap between cortical finger representations. Moreover, the projection patterns of corticospinal neurons and the characteristic connectivity within the primary motor cortex would not constitute the optimal foundation for strictly somatotopic movement control. Functional divergence and convergence have been shown to be basic principles of corticospinal architecture. Phillips et al. *(1977)* have demonstrated enormous convergence onto the spinal motor neuron pool of a given hand muscle from large M1 territories *(Phillips & Porter, 1977)*, and many studies have revealed that corticospinal neurons have direct connections to the motor neuron pool of multiple muscles *(Shinoda et al., 1979; Nudo et al., 1992)*. This prompts the question: Would a strict somatotopic basis for finger movement control make sense, and why are people placing so much effort on identifying such an orderly architecture? Given that the arm has four principal rotation points with many degrees of freedom and about 50 muscles to control reaching and grasping, as well as very highly skilled complex finger movements (as required in playing a musical instrument for example), a highly distributed and intermingled nature of functional M1 organization seems well suited to provide optimal and most efficient cortical control of those movements. It needs to be considered that there is coordinated action of certain muscles on different fingers and that movements of a given body part (e.g. one finger) necessarily occur in the context of stabilization of neighboring muscles, which may be also controlled by M1. Therefore, not only cortical but also biomechanical and postural constraints seem to undermine the very idea of a somatotopic arrangement. Also, the intermingled nature of the functional M1 architecture might be a better precondition for functional reorganization as induced by training or lesion.

8.5.3 Training related changes in between-finger relations

The main finding of the present study is a decrease in distances between centroids of finger-specific representations in M1 induced by an elementary motor training of the thumb. An enormous amount of work has already been designated to studying motor skill learning, but most of the studies used complex motor sequence learning or movement adaptation learning *(Sanes & Donoghue,*

2000). The focus of those studies was predominantly placed on *large-scale* changes, that is, learning-based changes in task-related neuronal networks *(Doyon & Benali, 2005)* or changes in the scaling of activation clusters in certain regions (like extent or intensity). Studies using brain imaging methods and focusing on training-dependent shifts of single finger representations within M1 / S1 are rare. One seminal paper, published by Elbert et al. (1995), reported enlarged distances between finger representations in the primary sensory cortex of professional violinists. While this finding was explicitly related to intensive musical practice by the violinists another study reported larger distances between dipole sources for different finger movements in the dominant compared to the subdominant M1 *(Volkmann et al., 1998)*. Although the authors emphasize the possibility that this asymmetry might be due to the different practice related skill levels of both hands, it cannot be ruled out that hand skill asymmetries are also determined by genetic influences *(Annett, 1964)*. Given the effect of enlarged motor and somatosensory hand representations following life-long training *(Munte et al., 2002)*, it appears from previous work that finger representations gradually move apart when capturing more cortical space. Thus, shifts of finger-specific cortical representations observed after life-long training are likely based on different principles than changes evoked by elementary motor training as used in the present study. High demands are placed on the motor system in order to accomplish repetitive tapping movements at maximum speed. As the task requires a highly individuated movement of the thumb, this may result in increasing demands to actively suppress movements of neighbouring fingers. Alternatively, the intense daily training of maximum thumb tapping speed may have indirectly affected remaining fingers. This is supported by the behavioural data showing some transfer of motor training to nearly all fingers of the trained hand. We did not use splints for the home-training that would have restricted overt movements of fingers not involved in the training. Taking enslaving effects *(Zatsiorsky et al., 2000; Aoki et al., 2003; Schieber & Santello, 2004)* and biomechanical constraints into account, we cannot exclude the possibility of accompanying movements. However, these movements primarily serve supportive and stabilizing functions, and can therefore be better classified as isometric movements. We deliberately decided against the use of a splint because of our

impression that a splint would not suppress the cortical efferences controlling finger movements or hinder the muscles from isotonically contracting within their constraint. Studies have also shown that even mental imagery of movements is sufficient to induce cortical activation in the motor areas and evoke plastic changes (Jeannerod & Frak, 1999).

We are aware of the fact that changes in location of the COM associated with a certain finger movement across different time points may be the result of insufficiently reliable measurements. Few studies have addressed this issue but all found a very high degree of consistency in functional finger representations *(Wexler et al., 1997; Carey et al., 2000a; Liu et al., 2004)*. A recent study by Alkadhi et al. (2002) addressed the issue of reproducibility of M1 somatotopy measured with fMRI *(Alkadhi et al., 2002a)*. They reported a high intra- and interindividual reliability of both large- and fine-scale somatotopy. In taking these studies into account, training-dependent shifts of finger-specific COMs are not likely to be a result of limitations in reliability.

Post-hoc correlation analysis was conducted to find a more conclusive explanation for the somewhat unexpected direction of changes and produced interesting findings. First, the neurophysiological training effect (decreased distances between cortical finger representations) negatively correlates with the behavioral training effect (decreasing ITIs). In other words, subjects showing large shifts of finger representations (from segregation to cortical overlap) do only show small practice-related increases in tapping speed. Second, there is a correlation between the initial finger representations with the behavioral training effect, allowing prediction of the amount of training gain on the basis of the initial finger representation. Subjects with intermingled overlapping finger representations exhibit small or no shifts of finger representations but strong gains in tapping speed, while, conversely, subjects with initially larger distances between finger representations show greater shifts, that is, a stronger decrease of those distances, and less gains in tapping speed.

This result provides support for the idea proposed by Schieber et al. *(2004, 1999)* that for several reasons (peripheral and central constraints) an intermingled and overlapping organization of finger representations would be a very efficient way to control individuated finger movements *(Schieber, 1999; Schieber & Santello, 2004)*. In addition, this conceptualization explains findings from previous studies showing increased segregation of finger representations as a consequence of life-long training (e.g., for professional musicians). Schieber proposes that segregated somatotopically organized central control of finger movements would be more efficient in case of increasing individuation of finger movements. Increased ability for individuated finger movement in terms of reduced enslaving effects can be observed in musicians vs. non-musicians, but also in untrained subjects when the dominant and non-dominant hands are compared. The reasons for subjects having different pretraining conditions were not addressed by the present study; certainly this is an issue that needs further exploration in the future. It is conceivable that subjects who show a pronounced reduction in between-finger distances over the course of training would also show large gains in performance. We can only speculate on this, but those subjects might simply need more training time in order to first meet the possible precondition of a highly interconnected overlapping control network.

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Section 9

GENERAL DISCUSSION & OUTLOOK

The aim of this thesis was to investigate activation, modulation and reorganization of the human sensorimotor cortex. While there is much evidence for tremendous effects of reorganization within the entire motor system due to complex motor skill learning, neural changes associated with adaptation/alteration of simple movement parameters in the context of motor practice have received little attention so far. The empirical part of this thesis was therefore designed with the following specific aims:

- *To assess changes in corticospinal excitability that accompany the intense, longer-lasting training of elementary movements of either the dominant or subdominant hand (▸Section 6)*

- *To study training-induced changes in neural activation during the performance of a given elementary movement involved in intense, longer-lasting practice (▸Section 7)*

- *To reinvestigate the functional organization of the hand motor area of the primary motor cortex with respect to the question of somatotopy, and more importantly, to explore training-induced changes of the pattern of functional finger representations which underlies movement control (▸Section 8)*

The key findings of these investigations and their implications will be summarized and integratively discussed below. Finally, a short conclusion and outlook for future work will be given.

9.1 A Summary of Results

All three experiments reported in ▸Sections 6, 7 and 8 have explicitly aimed to answer the question whether there are changes in the pattern of M1 activity accompanying an intense, longer-lasting training of elementary, non-sequential tapping movements. As outlined in the first sections, the issue of motor practice

has been addressed by an enormous number of studies; but the focus was placed on complex sequential movements in most cases. Furthermore, training durations typically used in such studies were rather short and did often not exceed one single training session (< 1h) *(Grafton et al., 1992a; Hazeltine et al., 1997; Shadmehr & Holcomb, 1997; Jueptner et al., 1997a; Toni et al., 1998; Grafton et al., 2002; Morgen et al., 2004; Garry et al., 2004; Floyer-Lea & Matthews, 2004)*. There are only very few studies in humans that have explored effects of trainings lasting for several weeks *(Pascual-Leone et al., 1994; Karni et al., 1995; Hlustik et al., 2004; Nyberg et al., 2006)*; all of them using complex movements.

In this thesis, transcranial magnetic stimulation (TMS), electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) were employed to assess training-related changes in neural activity. It is important to emphasize that these techniques differ in several aspects (see ▸Section 4 for details). One aspect that is of particular relevance for the present thesis relates to the temporal characteristics of the study designs linked with the different methods. TMS was applied 'off-line', that is corticospinal excitability was tested when the trained muscle was at rest (well after training). In contrast, fMRI and EEG (and corresponding alpha-band activity) were registered 'on-line' during the performance of the trained movement. Thus, in case of the present thesis, EEG and fMRI are used to analyze motor function directly related to the neural process of movement preparation and execution. TMS rather addresses effects that occur beyond the actual training period and which likely represent operations underlying training-induced performance gains similar to the concepts of motor consolidation *(Shadmehr & Holcomb, 1997; Muellbacher et al., 2002; Krakauer & Shadmehr, 2006)* and offline-learning *(Robertson et al., 2005; Press et al., 2005)* in M1. However, all techniques were exploited to uniquely contribute to answer the following overarching question: Given that M1 has been suggested to operate at maximum processing capacity during maximum speed movements, how does it manage to control the higher maximum tapping speed that is developing across training?

9.1.1 What happens to the contralateral M1 trough training?

The main result of the TMS study (▸Section 6) is a strong increase of corticospinal excitability (tested by TMS pulses applied to M1 contralateral to the trained hand) from pre- to posttraining measurements that accompanies significant training-induced speed gains. This is true regardless of whether subjects trained their dominant right or their subdominant left hand. It is important to again mention that the measurements were carried out at the resting muscle and in temporal distance to the training session (interval of several hours). Hence, the intense training seems to cause a higher transient baseline activity of the corticospinal fibers involved in training. In contrast, the EEG study revealed constant activation levels of M1 associated with the performance of the trained movement before and after training. Data obtained from fMRI show a similar pattern; activation volumes, defined as the number of significantly activated voxels, did not change with training. However, as in the TMS study, the maximum tapping speed was strongly increased after the 4 weeks of practice.

At first view, findings from fMRI and EEG may seem to be inconsistent with the results of the TMS study showing enhanced excitability (activation) when comparing post- to pretraining measurements. Having a closer look, there are several issues that may limit a direct comparison between the two findings and therefore may serve to explain the apparent inconsistency. As already mentioned above, TMS was applied off-line whereas EEG and fMRI both were registered in an on-line manner. As a consequence, increases in corticospinal excitability seen with TMS are not directly linked with the control of a given movement but rather reflect processes in M1 that take place beyond the physical practice. Increases in corticospinal excitability during the course of training, as measured with TMS, may constitute a necessary prerequisite for inducing plastic changes in the sensorimotor cortex. The rational behind this hypothesis is that increased excitability reflects higher neural activation, and higher neural activation in turn is known to enhance the build-up of new inter-neuronal connections and synapses. This leads to a strengthened efficiency of neural signaling. In the particular case of maximum-speed tapping movements, changes in contralateral M1 function induced by increased excitability may only be recognized

by the behavioral improvement. Increased efficiency of M1 after training would in that case be reflected by its ability to control higher movement rates with the same amount of activation as before training. In other words, training-related neural changes are masked by training-related changes in behavior.

9.1.2 What happens to the ipsilateral M1 through training?

Both, the TMS and the EEG study, show that training of the left, subdominant thumb influences activity patterns in the dominant left motor cortex, ipsilateral to the trained hand (This issue was not addressed by the fMRI study). The extent to which M1 is involved in controlling ipsilateral hand movements has been extensively studied in the past *(Kim et al., 1993; Chen et al., 1997b; Jäncke et al., 1998a; Baraldi et al., 1999; Cramer et al., 1999; Caramia et al., 2000; Alkadhi et al., 2002b; Kobayashi et al., 2003; Huang et al., 2004; Verstynen et al., 2005; Lutz et al., 2005)*. It was consistently shown that the dominant motor cortex is involved in the control of movements of both hands, while the sub-dominant motor cortex is only activated with contralateral movements. There have been only very few investigations of asymmetrical hemispheric involvement in the context of motor practice/skill learning to date *(Halsband, 1992; Schulze et al., 2002)*. Data resulting from the EEG study, reported in ▸Section 7, indicate a reduction of activity across training. Findings from the TMS study (▸Section 6) additionally show that the left M1 shows a strong increase of activation, and thus seems to be particularly involved (recruited) during the first training days. These findings highlight the importance of the dominant hemisphere in controlling subjects' maximum tapping speed when the right hemispheric motor system is not yet fully capable of controlling effortful movements of the subdominant hand. Consistent with this interpretation, ipsilateral M1 activity should diminish as the subdominant right M1 becomes more *efficient* during the course of training. Both studies do provide supporting evidence for this hypothesis; showing a reduction of M1 activity from pre- to posttraining as reflected by increased alpha-band activity and reduced corticospinal excitability.

9.1.3 Banishing the motor homunculus to reach a better motor performance

The primary objective of the third experiment (▸Section 8) was to explore if and how the pattern of finger-specific movement representations changes with practice. Given the dominance of the homuncular idea and the big debate on that issue going on for more than a decade, I will first address how the present data contribute to this debate. Based on the concept of the motor homunculus, that has been introduced by Wilder Penfield in 1950 *(Penfield & Rasmussen, 1950)*, several studies have investigated whether or not a fine-scale somatotopy of finger representations within the human hand area exists. In summary, previous studies have one finding in common, that is extensive overlap of cortical finger representations. Beyond the finding of strong overlap, some studies have provided evidence for a somatotopic gradient *(Kleinschmidt et al., 1997; Lotze et al., 2000; Beisteiner et al., 2001; Hlustik et al., 2001; Dechent & Frahm, 2003; Beisteiner et al., 2004)* while others have challenged this idea *(Schieber & Hibbard, 1993; Sanes et al., 1995; Schieber & Poliakov, 1998; Volkmann et al., 1998)*. The data of experiment 3 corroborate earlier findings of extensive overlap; however, the centroids of finger-specific representations appeared to be reliably distinguishable from each other. Evidence for a somatotopic organization of all five fingers in the homuncular sense was only weak (see ▸Section 8 for details). Instead, our data provide strong support for an individual organization of strongly overlapping functional finger representations. The adequateness of an intermingled arrangement of finger representations is supported by several findings. First, substantial horizontal connections span M1 and provide interconnections between neuronal ensembles associated with different muscles. Second, the mapping between upper motor neurons in M1 and lower motor neurons in the spinal cord is characterized by convergence and divergence, and is therefore enormously complex. Furthermore, highly complex finger movements demand extensive intracortical communication *(Sanes & Donoghue, 2000)*.

As a new aspect, experiment 3 assessed training-induced changes of cortical finger representations with high-resolution fMRI. The main finding here was that the entire cortical arrangement of finger representations is changed by a simple motor training of only one single finger. Interestingly, the training led to a gen-

eral reduction of distances between finger-specific representations in M1 contralateral to the trained hand. Moreover, correlations between behavioural and neural changes were identified. First, the extent of reduction of between-finger distances across training was negatively correlated with the extent of speed gain. Second, the level of segregation of finger representations before training (as reflected by the magnitude of between finger distances) predicted the extent of speed gain achieved as a result of training. In other words, the smaller the distances between finger representations before training, the smaller the changes in the arrangement of finger representations and the larger the training-induced speed gain. On the other hand, a more distinct segregation of finger representations before training is accompanied by stronger reductions of between-finger distances and small speed gains. It therefore is tempting to conclude that a cortical organization that maximizes overlap and interlacing of neural tissue is favorable for selectively tapping a finger at maximum speed.

In conclusion, study 3 contributes to the issue of training-induced changes in M1 by suggesting that a particular functional configuration of the 'system' might be favorable or even a precursor for distinct increases in motor performance. This is a new finding that would have far-ranging implications (especially in the clinical and rehabilitation context), and therefore necessarily requires further empirical approval.

9.1.4 A technical issue: How LORETA works for the motor domain

One specific aim of Study 2 was the intracortical localization of rate-related alpha-band activity to further validate the LORETA method (Low Resolution Brain Electromagnetic Tomography) in the motor domain. The LORETA method has been previously validated through correct localization of epileptic foci, primary sensory, language and face processing areas *(Pascual-Marqui et al., 2002)*. The results of Study 2 do convincingly show that LORETA localizes rate-related alpha-band activity bilaterally in the sensorimotor cortex. This result provides clear further evidence for the validity of the LORETA method.

9.1.5 Potential problems or pitfalls

As it is the case for nearly every empirical study, there are some problems also for the present studies that may limit the explanatory power and therefore should be addressed. One very important issue relates to the number of subjects in the context of long-term training studies. Several obvious problems complicate such studies at almost all stages: it hampers the acquisition of subjects, the implementation of the experiment and also statistical data analysis. The biggest problem certain is to ensure constant levels of motivation in the subjects. This problem is particularly relevant for the present studies since the trained movement consisted of 'boring', repetitive, thumb tapping movements. Furthermore, the training was carried our on the subjects' home computers. We therefore attached great importance on the selection and instruction of the subjects in order to ensure study compliance. In addition, the training was guided by a computer-program that was implemented to make the training situation a little competitive and therefore exciting (subjects always saw a counter that provided online feedback of how many key presses subjects accomplished in a give trial). Furthermore, the little number of subjects usually assessed in long-term training studies does limit the statistical power. To handle this problem, it has been suggested to calculate effect sizes in addition to standard parametrical tests to be able adequately evaluate the strength of a given effect *(Cohen, 1988)*. A second point concerns the behavioral control of the trained movement during the training as well as during performance assessment. One may criticize that no splint has been used in the experiments of this thesis to immobilize muscles not involved in the training. However, it was a deliberate decision against the use of a splint because of our impression that a splint would not suppress the cortical efferences controlling finger movements or hinder the muscles from isotonically contracting within their constraint. Given that this issue is extensively discussed in ▸Section 8.4 it will not be further addressed at this place.

9.2 Implications for Future Work

The work presented in this thesis establishes several important findings. However, many interesting issues still remain to be addresses and new questions have arisen from the findings of this thesis.

New interesting questions arise primarily from the findings of ▸Section 8. First of all, the negative correlation between the degree of segregation of finger representations and the behavioral speed gain needs replication and validation. It would be further interesting to explore similar correlations in case of right- (dominant) hand training. It appears from the data that subjects have different pretraining conditions with regard to the distances between finger-specific movement representations; however, possible reasons for this variance were not addressed in this thesis. Hence, this important issue certainly needs further exploration in the future. Another issue relates to subjects with large inter-finger distances before training who show a large training-induced effect on the neural level (strong decrease of such distances), but at the same time training gains were small. As already discussed in the corresponding publication in ▸Section 8, it is conceivable that these subjects can also show large behavioral improvements, but at a later point in time. So far only speculations are possible: subjects with stronger segregation before training might simply need more training time in order to first meet the possible precondition of a highly interconnected overlapping control network. Shifts of finger representations in M1 / S1 as a result of extensive training have been intensely discussed in the context of patients suffering from focal dystonia. The fusion of finger representations in the sensorimotor cortex, and thus the dedifferentiation of sensory feedback information, has been suggested being one likely cause of the disease *(Munte et al., 2002)*. Similar maladaptive mechanisms of plasticity have been proposed for the motor cortex in dystonic patients. However, the success of symptomatic therapeutic approaches that have already been tested is neither convincing nor satisfying. Studies of sensorimotor retuning as introduced by Candia et al. *(2002)*, but also studies based on other sensorimotor re-training programs, for instance after stroke *(for a review see Hakkennes & Keating, 2005)*, report inconsistent results.

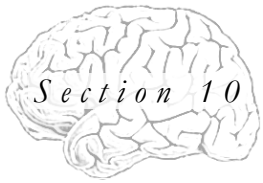
Thus, it might be helpful and necessary to first elucidate the particular pattern of functional finger representations in M1 in dystonic patients before effective therapy programs can be designed and conducted.

Another issue that needs exploration concerns the time course of facilitation effects in TMS after the training has been finished. Pertinent literature places the focus on postexercise facilitation and depression phenomenon over a short timescale. It is still unclear for how long changes in corticospinal excitability (as induced during longer training intervals, e.g., several weeks) persist and if there is a direct relationship between the duration of training and the duration of persistence of enhanced excitability.

Shifting the focus towards more methodological questions, results from experiment 2 provide strong support for the validity of the LORETA solution in the motor domain. Most EEG data published on motor control and motor learning relate to surface EEG. The well-known problems of surface EEG make tools such as LORETA, and particularly their continuous advancements, absolutely necessary. Considering the 'rate effect' that was replicated in experiment 2, the next step would now be to correlate LORETA solutions with surface EEG data, and even more importantly to relate both measures to behavioral variables to explore whether LORETA has advantages over surface EEG with respect to the extent it contributes to our understanding of how the brain works.

When reviewing current neuroscience literature, there is a general move towards the combination of neuroscientific methods with the underlying idea to exploit the advantages of the single techniques to boost the gain of new insights or to cross-validate classical findings. Successful combinations, for instance of fMRI and EEG or fMRI and TMS, are promising and will contribute to deepen and to extend our understanding of brain function in the future. Many interesting and important questions are waiting to be answered.

But that, of course, is another story…



Section 10

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ACKNOWLEDGEMENTS

First of all, my acknowledgement applies to Lutz Jäncke who awakened my interest in neuroscience with his incredible enthusiasm for this domain. During my PhD time in Zurich, he gave me the freedom to do my own thing but was always generous with his valuable time and ideas and advice whenever it was needed (despite being the busiest man on earth).

Special thanks go to my parents for their continuous encouragement and support. They made me feeling confident of mastering the challenge of this thesis just by believing in me.

Kai Lutz provided unpayable support throughout the entire three years. He was a constant source of support & inspiration and made this thesis possible.

Special thanks to Petra Jäncke for having a great time together sharing the office and for always having an open ear for problems (also non-scientific).

Simon Baumann earns a more general acknowledgement for many fruitful discussions, for the endless time he spend to explain me the basics of neuroimmunology, and for constantly finding ways to convince me to spend days on the snowboard which helped to provide energy to return to work.

Julia Blum maintained my sanity. Special thanks to her for just being there when needed. That *REALLY* helped a lot.

Martin Meyer has to be mentioned here given that he is just such a great colleague!

Michaela Essen introduced me to the EEG technique. She has been a very nice and fun colleague over the last 3 years.

Special Thanks to Nicole Ehrhorn as she provided the necessary emotional support outside the field of science.

Daniel Eicke needs to be mentioned for two reasons… first, because he is a very close and special friend and, second, because he helped with some of the figures (he made these cool proton spin pictures in section 4.2.1).

Marcus Cheetham spent (presumably) painful hours to revise my paper manuscripts struggling with my *deficient* English language skills.

Conny Schmidt provided support with her valuable physicist knowledge and trained me to operate the scanner – thereby granting me the opportunity to while away whole nights and partly weekends at the console.

Ulf Ziemann proofread the paper resulting from the TMS study and provided helpful comments to it.

Uwe Herwig deserves specific acknowledgement for playing a crucial role in instructing me how to use TMS.

Simply thanks to anyone who helped and supported me during those years of being doctoral student…

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Publications (peer-reviewed)

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